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# *Ortho*-Substituted Arylsilanes in Oxidative Gold Catalysis



THE UNIVERSITY  
*of* EDINBURGH

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*Doctor of Philosophy*

University of Edinburgh

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## Declaration

I declare that the work in this thesis was carried out by myself under the supervision of Prof. Guy Lloyd-Jones FRS and is in accordance with the requirements of the University of Edinburgh. This work is original, except where indicated by special reference in the text, and no part of the thesis has been previously submitted for any other academic award.

Signed .....

Date .....

## Abstract

Organometallic compounds derived from tin, boron, and zinc, have been used extensively in transition metal-catalysed cross-coupling, and continue to hold status as the go-to reagents to form new carbon-carbon bonds. Recently, organosilicon compounds have emerged as an attractive alternative to these established reagents, benefitting from low toxicity, low cost, and general ease of handling. While the fundamental reactivity of arylsilane reagents ( $\text{Ar-SiR}_3$ ) is well known, their role in transition metal-catalysed reactions is generally less well studied.

This thesis comprises an investigation into the effect of *ortho*-substitution of these arylsilane reagents, and specifically, their application in gold-catalysed direct arylation. In Chapter 2, the transmetalation of these reagents to gold(III) is assessed using a combination of *in situ* reaction monitoring coupled with kinetic simulations. This allowed a scale of reactivity to be constructed for a range of structurally diverse arylsilanes, and uncovered that more sterically hindered arylsilanes actually exhibit accelerated rates of transmetalation.

In Chapter 3, the reactivity of *ortho*-substituted arylsilanes in gold-catalysed arylation is addressed. The majority of arylsilanes tested in the previous chapter were found to be unable to undergo coupling, despite the viability of transmetalation having been demonstrated. Slight modification of the *ortho*-substituent, to incorporate a tethered ligand, was found to have a dramatic effect on reactivity, and allowed the coupling of a variety of substrates. The nature of the ligand, as well as the substitution of the tether was found to have a significant impact on the rate of coupling.

Chapter 4 describes the way in which the reactivity of *ortho*-substituted arylsilanes might be exploited in a “Catch and Release” protocol for catalyst recovery. This aims to combine the established benefits of homogeneous and heterogeneous catalysis to offer an alternative to current methods of catalyst recycling in industrial chemistry. A number of different “Catch and Release” mechanisms were considered, and the validity of the concept was demonstrated in a monophasic system.

## Lay Summary

The ability to construct complex molecules lies at the heart of synthetic chemistry, allowing scientists to create chemical compounds that can be used for a multitude of applications throughout modern-day life. The advent of metal-catalysed cross-coupling in the late 20<sup>th</sup> century has revolutionised the way in which synthetic chemists conceptualise and construct molecules, providing a method to synthesise hugely important, but often challenging, carbon-carbon bonds. The field of cross-coupling remains vibrantly active to this day, with initiatives to reduce manufacturing costs and the environmental impact of chemical synthesis driving the continued development of new and improved synthetic methods.

Previous research in the Lloyd-Jones group described a novel gold-catalysed cross-coupling reaction that relies on the use of silicon-containing reagents (arylsilanes). These are an attractive class of chemical feedstock due to their ease of preparation, low toxicity, and amenability to long-term storage. While the practical advantage of these reagents is well documented, their application in catalysis is somewhat limited, and the exact way in which they react (the reaction mechanism) is often poorly understood.

The work in this thesis aims to describe how these compounds behave under the conditions of gold catalysis, and to highlight the profound effect that minor structural modifications to the arylsilane reagent can have. This is expected to be of broad benefit to those attempting to apply the chemistry to the synthesis of complex molecules, while providing fundamental mechanistic understanding that can be exploited in the development of future methodologies.

## Acknowledgements

The research documented in this thesis is the result of a thoroughly enjoyable, challenging, and rewarding time spent in the Lloyd-Jones research group in Edinburgh. I owe much to the supervision of Prof. Guy Lloyd-Jones, who has an admirable passion for science, and has invested a great deal of time in my training as a physical organic chemist. His approach to problem-solving and rigorous attention to detail (and email) have been an inspiration during the course of my studies.

I have been lucky to work alongside an incredibly talented group of scientists and friends during my PhD; to simply list them would be a disservice to the amount of help, guidance, and support that they have offered both in and out of the lab. I am particularly grateful to Liam and Tom, both of whom were always willing to answer my naïve questions about gold catalysis and reaction kinetics. Life in the research group has provided me with many happy memories, and I'll look back with particular fondness on the varied lunchtime discussion, occasional sporting triumphs, and regular Elton John Fridays.

I would like to thank the various technical support staff at the University of Edinburgh, particularly Lorna and Juraj who have so often come to the rescue when I've needed help with the maintenance of our group NMR spectrometer.

Finally, I'd like to acknowledge the importance of my family and friends throughout the course of my academic life to date. Studying towards a PhD has not always been easy, and they have offered a source of constant respite when needed. While they may not understand what an *ortho*-substituted arylsilane is, they have contributed far more to this piece of work than they are likely aware.

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## Abbreviations

Ac	acetyl
AcOH	acetic acid
Ar	aryl
Bn	benzyl
cm <sup>-1</sup>	wavenumber
Cs	camphorsulfonate
CSA	camphorsulfonic acid
Cy	cyclohexyl
d.r.	diastereomeric ratio
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
E, E <sup>+</sup>	electrophile
equiv	molar equivalents
ESI	electrospray ionisation
Et	ethyl
EtOH	ethanol
g	gram
H	enthalpy
HCIB	[hydroxy(camphorsulfonyloxy)iodo]benzene
het	heteroaryl
HMDS	hexamethyldisilazane

HPDMS	3-hydroxypropyldimethylsilyl
HRMS	high resolution mass spectrometry
Hz	hertz
IBDA	iodobenzene diacetate
<i>i</i> -Pr	isopropyl
IR	infrared
K	equilibrium constant
<i>k</i>	rate constant
KIE	kinetic isotope effect
L	neutral ligand; litre
LDA	lithium diisopropylamide
M	molar
m.p.	melting point
<i>m/z</i>	mass-to-charge ratio
Me	methyl
MeOH	methanol
mg	milligram
MHz	megahertz
mL	millilitre
mmol	millimole
mol	mole
mol%	mole percent
MS	mass spectrometry
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide

<i>n</i> -Bu	normal butyl
NMR	nuclear magnetic resonance
Nu, Nu <sup>-</sup>	nucleophile
Ph	phenyl
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
pin	pinacolato
Piv	pivaloyl
ppm	parts per million
PTLC	preparative thin layer chromatography
R	alkyl, aryl, or heteroaryl substituent
rt	room temperature
S	entropy; substrate
S <sub>E</sub> Ar	electrophilic aromatic substitution
t	time
T	trap
<i>t</i> -Bu	tertiary butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
tht	tetrahydrothiophene
TLC	thin layer chromatography
TMS	trimethylsilyl
w/w	by weight

WI	Wheland intermediate
X	halide; anionic ligand
$\delta$	chemical shift
$\mu\text{L}$	microlitre
$\rho$	Hammett reaction constant
$\sigma$	Hammett substituent constant

### Introduction

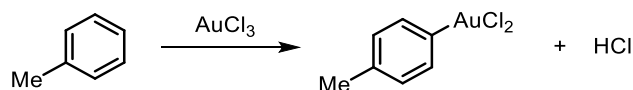
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## 1.1. Oxidative Gold Catalysis in Organic Synthesis

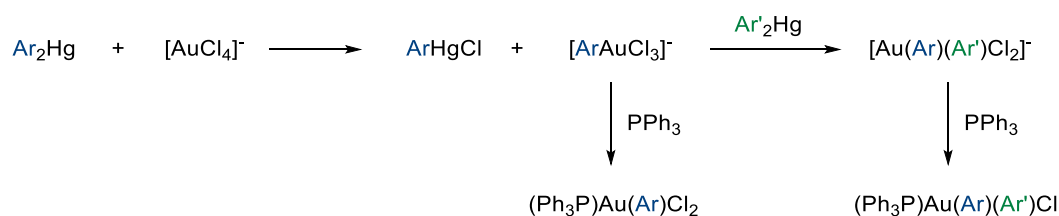
### 1.1.1. Reactivity of Gold Complexes

It has long been known that gold(III) complexes are capable of formally activating aryl C-H bonds. The earliest reports by Kharasch and co-workers date back to the 1930s, and describe the auration of simple aromatic compounds with anhydrous  $\text{AuCl}_3$  to generate the corresponding arylgold(III) complexes (Scheme 1.1).<sup>1</sup> Over the following 80 years, a number of reports expanded upon these findings to offer access to a variety of functionalised gold(III) arene complexes, using stoichiometric quantities of gold(III) precursors with stabilising ligands.<sup>2-5</sup> Electrophilic auration of arenes is regioselective, with the site of substitution governed by the established rules of electrophilic aromatic substitution ( $\text{S}_{\text{E}}\text{Ar}$ ).<sup>6</sup>



**Scheme 1.1.** Formal C-H activation of toluene by gold(III) chloride reported by Kharasch in 1931.<sup>1</sup>

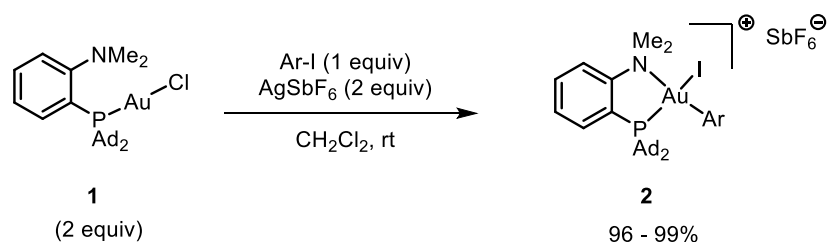
Other methods of arylgold(III) formation have utilised organometallic reagents such as organomercurials ( $\text{R}_2\text{Hg}$ ) to transfer aryl groups to gold(III) *via* transmetalation (Scheme 1.2).<sup>7-10</sup> Vicente and co-workers demonstrated that the resultant arylgold(III) complexes can be isolated in neutral form by substitution of a chloride anion for a suitable ligand (e.g.  $\text{PPh}_3$ ). Alternatively, addition of a second equivalent of  $\text{R}_2\text{Hg}$  allows access to either symmetrical or unsymmetrical diarylgold(III) complexes *via* the same protocol. These *cis*-diarylgold(III) complexes can undergo reductive elimination to form symmetrical or unsymmetrical biaryls, one of the key elementary steps in many transition metal-catalysed reactions.<sup>11</sup>



**Scheme 1.2.** Synthesis of arylgold(III) complexes by transmetalation from organomercury reagents.

Building upon the earlier work of Vicente, a number of alternative methods to generate arylgold(III) species have since been developed, typically involving transmetalation from organometallic reagents derived from tin,<sup>12</sup> lithium,<sup>13</sup> boron,<sup>14</sup> and silver.<sup>13</sup>

Although gold(I) is isoelectronic with platinum(0), the two metals exhibit strongly contrasting reactivity. Few literature reports of oxidative addition into aryl halides or *pseudo*-halides exist for gold(I), a consequence of the high oxidation potential of Au(III).<sup>15,16</sup> State-of-the-art examples include the use of rigid cis-chelating ligands,<sup>17,18</sup> intramolecular delivery,<sup>19</sup> photo-activation,<sup>20</sup> and hemi-labile (P,N)-ligands<sup>21</sup> to promote the oxidative addition of aryl iodides (Scheme 1.3).<sup>i</sup> However, the generality of these procedures in their current state is somewhat limited, and as a result very few gold-catalysed reactions depend on an oxidative addition sequence.

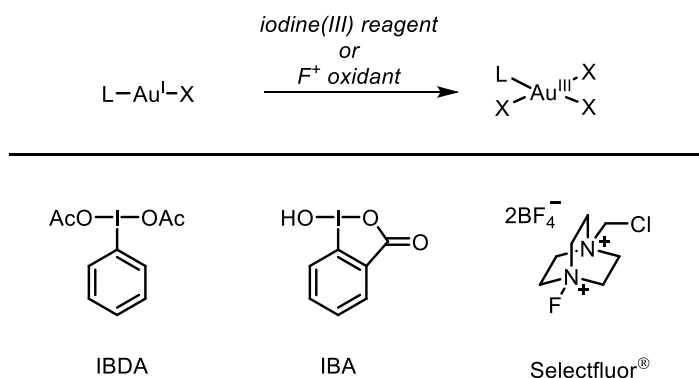


**Scheme 1.3.** Bourissou's method to promote gold(I) oxidative addition using stabilising hemi-labile (P,N)-ligands.

More commonly, redox based gold catalysis relies on the use of sacrificial, strong  $2e^-$  oxidants that are able to promote the oxidation of gold(I) to gold(III).<sup>22–25</sup> Hypervalent iodine(III) species, as well as electrophilic “F<sup>+</sup>” sources, have been established as the most general reagents to facilitate the oxidation in both stoichiometric<sup>26–28</sup> and catalytic<sup>29–31</sup> examples (Scheme 1.4).<sup>ii</sup>

<sup>i</sup> Toste and co-workers have also reported an oxidative addition into a highly strained C-C bond.<sup>139</sup>

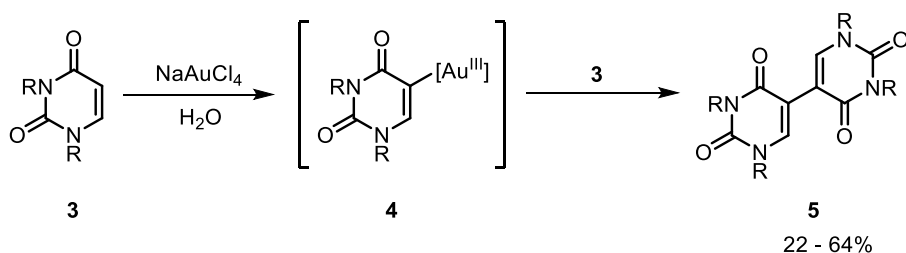
<sup>ii</sup> Oxidation with the molecular halogens (Br<sub>2</sub>, Cl<sub>2</sub>) is also possible, though rarely used in catalysis.<sup>140</sup>



**Scheme 1.4.** Common reagents used for gold(I) to gold(III) oxidation.

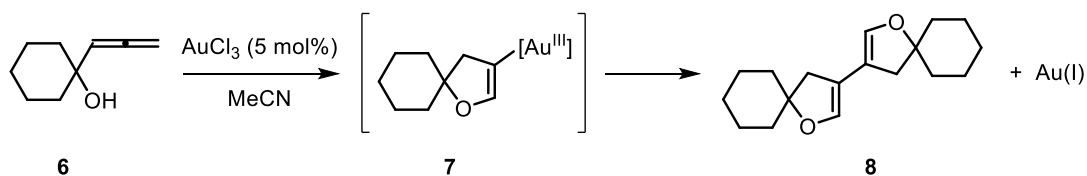
### 1.1.2. Stoichiometric Examples of Oxidative Coupling

Lippert and co-workers reported the homodimerisation of uracil derivatives in the presence of a stoichiometric quantity of Au(III) (Scheme 1.5).<sup>32</sup> Isolation of aurated uracil complex **4** provided evidence for initial activation of a C(sp<sup>2</sup>)-H bond, followed by oxidative coupling to form the corresponding dimer **5**.



**Scheme 1.5.** Oxidative dimerisation of uracil derivatives mediated by gold(III).

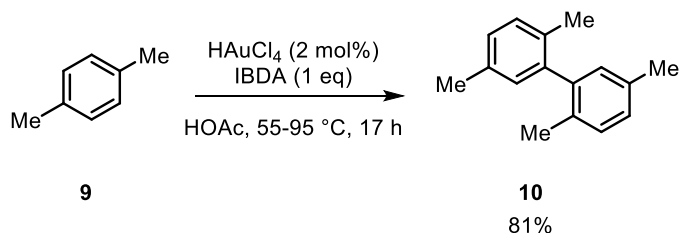
Hashmi and co-workers described an oxidative coupling by gold(III), when identifying one of the by-products of a desired cyclisation reaction as hydrofuran dimer **8**, resulting from the homocoupling of intermediate **7** (Scheme 1.6).<sup>33</sup> As in the work of Lippert, due to the absence of an external oxidant the coupling is not catalytic, and the product was only formed in stoichiometric quantities relative to gold.



**Scheme 1.6.** Identification of a by-product arising from oxidative homocoupling.

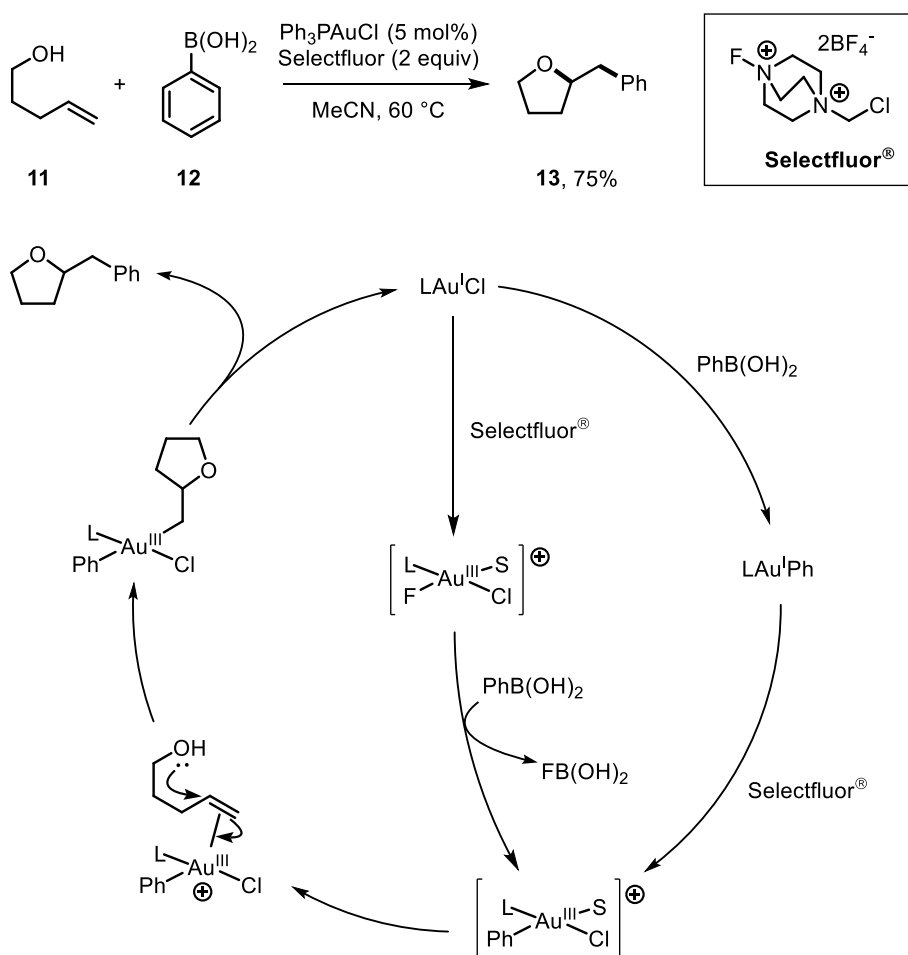
### 1.1.3. Applications in Catalysis

The first gold-catalysed homocoupling of electron rich arenes was reported by Tse and co-workers in 2008 (Scheme 1.7).<sup>34,35</sup> Using 2 mol%  $\text{HAuCl}_4$  as a catalyst, and iodobenzene diacetate (IBDA) as a stoichiometric oxidant, a variety of symmetrical biaryls could be synthesised in reasonable yield. Aryl halides were well tolerated, even under quite forcing conditions (95 °C, AcOH), highlighting the potential complementarity between gold- and other transition metal-catalysed transformations. In some cases, mixtures of regioisomers were obtained, as would be expected for selectivity governed by an  $\text{S}_{\text{E}}\text{Ar}$  mechanism.



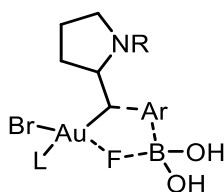
**Scheme 1.7.** Gold(III)-catalysed oxidative homocoupling of arenes.

As the homocoupling of arenes has limited utility in synthesis, the use of oxidative gold catalysis to effect similar heterocoupling processes has been the focus of much attention. Zhang and co-workers successfully demonstrated that arylboronic acids could be used as coupling partners in an oxidative gold-catalysed arylheterofunctionalisation of alkenes (Scheme 1.8).<sup>30</sup> Selectfluor® was used as a stoichiometric oxidant in this case, proposed to oxidise gold(I) with simultaneous formation of a gold(III) fluoride. It remained unclear however, whether this oxidation occurred prior to or directly after initial transmetalation from the boronic acid.



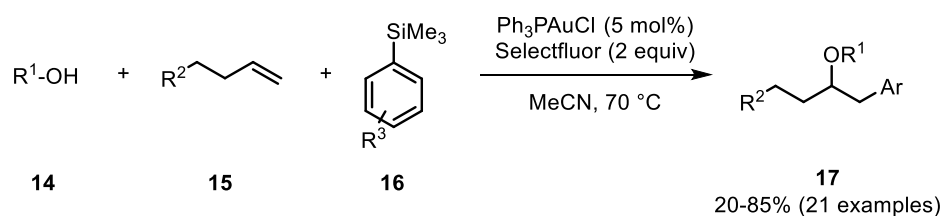
**Scheme 1.8.** Zhang's proposed mechanism for the oxidative carboheterofunctionalisation of alkenes using Selectfluor<sup>®</sup> as a sacrificial oxidant.

Toste and co-workers reported a variation of the reaction, together with a mechanistic investigation, in which  $[\text{dppm}(\text{AuBr})_2]$  was identified as an improved catalyst.<sup>31,36–38</sup> It was proposed that reductive elimination occurs *via* a bimolecular interaction en route to the transition state rather than from a formal arylgold(III) intermediate (as had been suggested by Zhang). Evidence in support of this focused on the inability of  $\text{Ph}_3\text{PAuPh}$  to act as an aryl donor in the absence of a suitable boronic acid. The isolation of an arylgold(III) fluoride species and its reactivity in the aforementioned coupling reaction was later documented.<sup>39</sup> It was identified that the gold(III) fluoride has an important role in coupling, presumably through activation of the arylboronic acid.



**Figure 1.1.** Toste's proposed bimolecular reductive elimination.

The scope of this coupling was simultaneously expanded by the groups of Toste,<sup>40</sup> and Lloyd-Jones,<sup>41</sup> to use aryltrimethylsilanes in place of boronic acids as the organometallic component (Scheme 1.9). The reaction is quite general, and tolerates a range of different alcohols, alkenes, and substituted arylsilanes as coupling partners. Interestingly, biphenyl derivatives, arising from homocoupling of the arylsilane reagent, were typically observed by-products in 3-5% yield. In contrast, the anticipated products of other side reactions, such as protodeauration and fluorination, could not be detected.

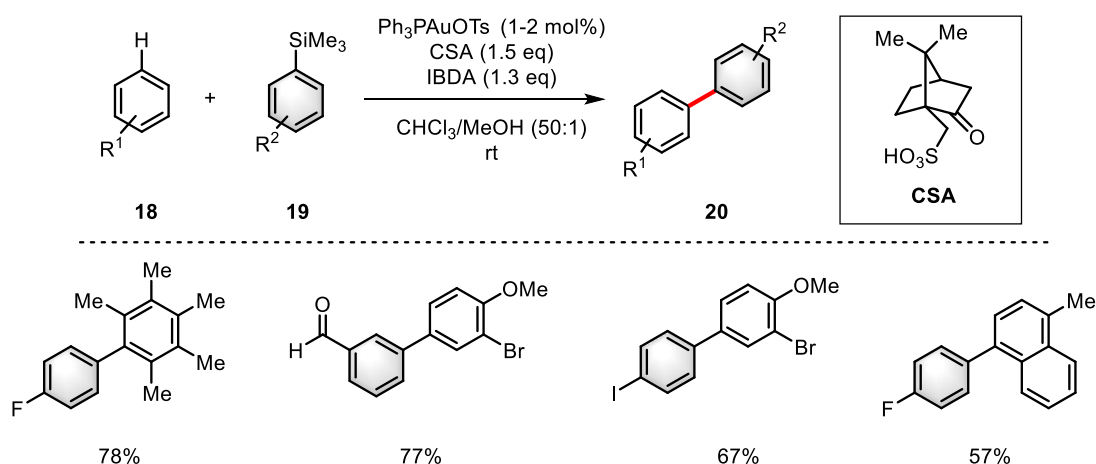


**Scheme 1.9.** Three-component oxyarylation of terminal alkenes *via* oxidative gold catalysis.

## 1.2. Gold-catalysed Biaryl Forming Reactions

### 1.2.1. Direct Arylation of Arylsilanes

Following the successful application of aryltrimethylsilanes in oxyarylation chemistry, Lloyd-Jones and co-workers disclosed the first oxidative gold-catalysed coupling of arylsilanes and arenes to form functionalised biaryls (Scheme 1.10).<sup>42</sup> The reaction proceeds at room temperature, with no necessary precaution to exclude oxygen, and a range of electronically diverse aryltrimethylsilanes and  $\pi$ -rich arenes can be used. Iodobenzene diacetate (IBDA) was identified as the most effective stoichiometric oxidant with camphorsulfonic acid (CSA) as an additive. The addition of methanol as a co-solvent was required to facilitate solubility of the multi-component system. Extensive substrate screening identified that oxidatively sensitive groups, along with aryl halides were tolerated under the reaction conditions.



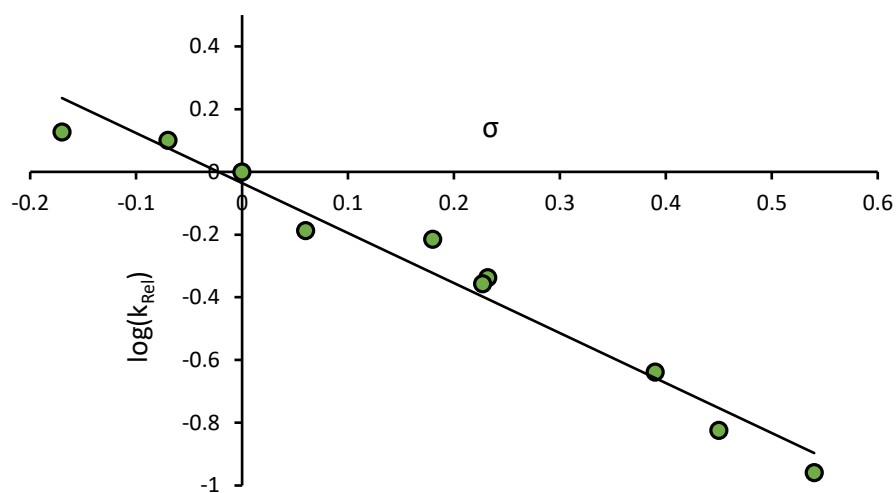
**Scheme 1.10.** Oxidative gold-catalysed arylation of arylsilanes and representative examples of accessible products.

Subsequently, a detailed mechanistic study was published in which the origin of selectivity and detailed catalytic cycle were proposed.<sup>43</sup> Tetrahydrothiophene gold(III)bromide ( $\text{thtAuBr}_3$ ) was demonstrated to be an improved pre-catalyst, with evidence that the previously used phosphine ligand was simply oxidised to the phosphine oxide during catalyst activation.<sup>iii</sup> The exact ligation of the active catalyst in solution is unknown, and with a range of weakly co-ordinating species present (MeOH, CSA, arene  $\pi$ -complexes, camphorsulfonate), is

<sup>iii</sup> The tht ligand is also consumed during catalyst activation, but oxidation occurs rapidly such that no induction period is observed.

anticipated to vary throughout the catalytic cycle, similar to the concept of ‘Serial Ligand Catalysis’ pioneered by White and co-workers.<sup>44</sup>

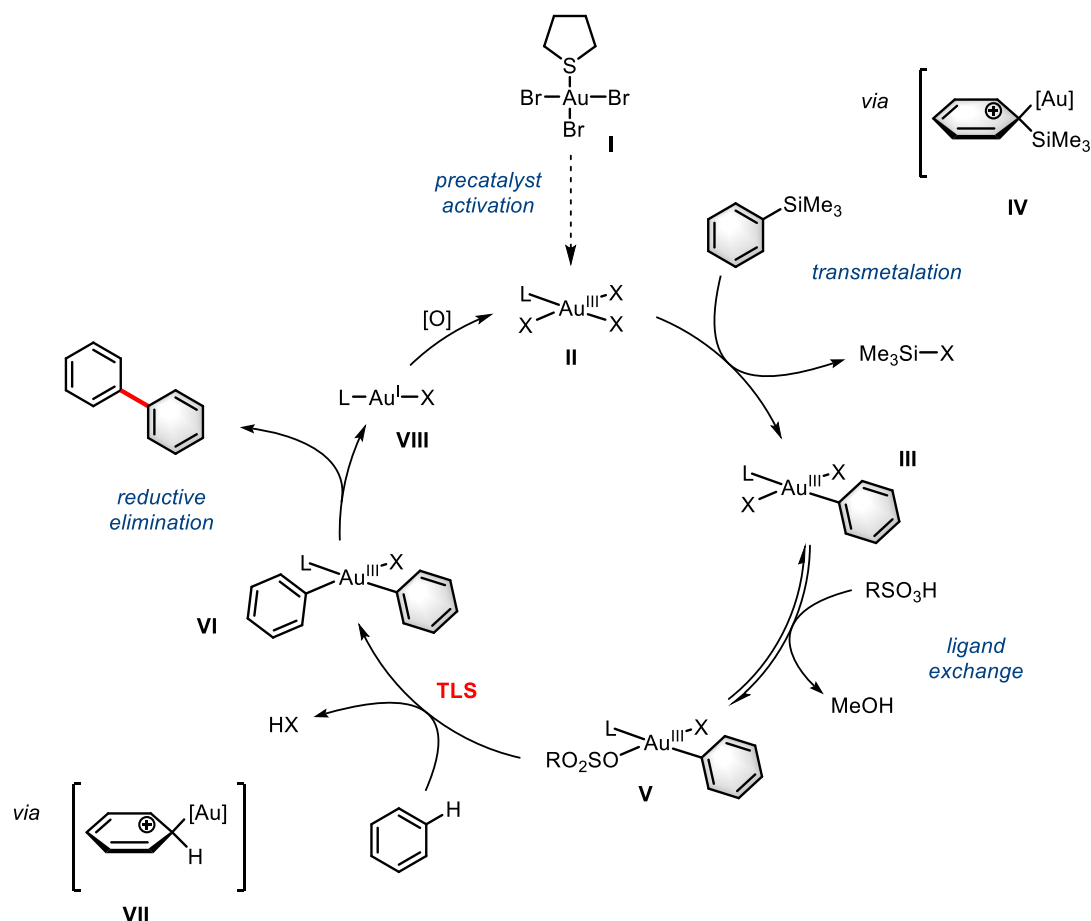
The regioselectivity of both silane and arene is predictable; arylsilanes are known to undergo aromatic substitution almost exclusively at the *ipso*-position due to the ability of the silicon group to stabilise  $\beta$ -cations.<sup>45</sup> While transmetalation of aryl groups to gold(III) is reasonably well documented, the mechanism of transmetalation from aryl silanes has not been studied in detail. It is proposed that in similar Pd(II) and Pt(II) chemistry, arylsilanes react in an  $S_EAr$  type mechanism.<sup>46,47</sup> Hammett analysis of the transmetalation to gold(III) was found to correlate with  $\sigma$ , corresponding to a value of  $\rho = -1.6$  (Figure 1.2).<sup>43</sup> The observation that electron-releasing substituents accelerate the rate of transmetalation is consistent with an electrophilic aromatic substitution mechanism of transmetalation.



**Figure 1.2.** Hammett analysis of the transmetalation from arylsilane to gold(III).

The site of auration of the arene is dictated by the rules of classical electrophilic aromatic substitution. In cases where more than one C–H bond is similarly activated, mixtures of regioisomers are obtained.

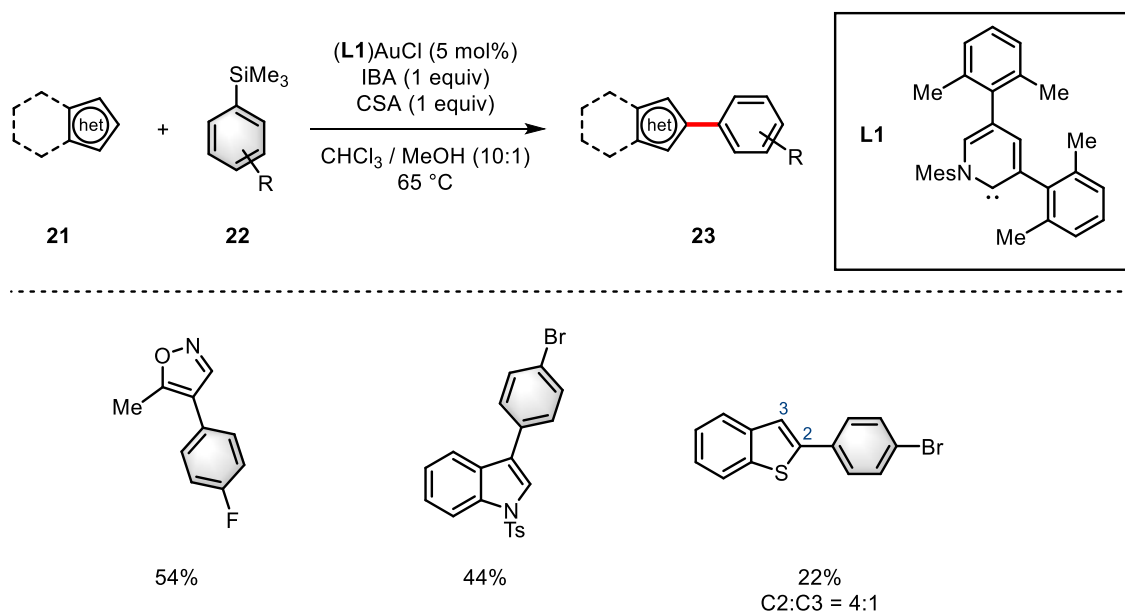




**Scheme 1.11.** Established catalytic cycle for intermolecular gold-catalysed direct arylation.

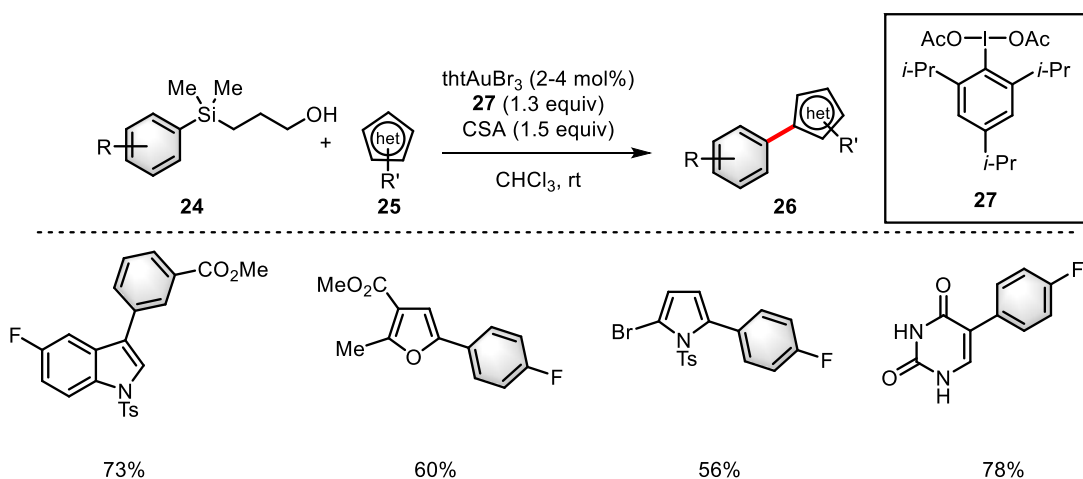
Extensive experimental evidence suggests that, following irreversible pre-catalyst activation, the arylsilane undergoes an electrophilic auration by a ‘ligand-free’ gold(III) species (**II**) (Scheme 1.11). The origin of chemoselectivity in this step is determined by the irreversible formation of a Wheland intermediate (**IV**), in which the silane is able to outcompete the arene due to stabilisation of this intermediate through the β-silicon effect. Removal of the trimethylsilyl group by MeOH affords an arylgold(III) species. Substitution of a ligand for camphorsulfonate is needed in order to generate the more electrophilic gold species **V** prior to the second (turnover-limiting) auration, leading to an inverse dependence on MeOH in the overall rate law. Unlike initial auration of the silane, π-complexation is now irreversible, leading to chemoselectivity for the π-rich arene in the second auration. Following Wheland intermediate formation (**VII**) and subsequent dissociation of a ligand, reductive elimination can occur from a 3-<sup>48,49</sup> or 4-<sup>50</sup> coordinate complex to form the heterocoupled biaryl and gold(I) species, **VIII**. Rapid oxidation then occurs to regenerate the initial gold(III) species and close the catalytic cycle.

Itami and co-workers reported a variation of the reaction in which NHC ligand **L1** was able to promote the coupling of a range of heteroarenes, albeit in modest yield (Scheme 1.12).<sup>51</sup> A slightly higher catalyst loading (5 mol%) and elevated temperature (65 °C) were found to be optimal in this instance. PPh<sub>3</sub>AuCl was also demonstrated to be catalytically competent, though led to a significantly reduced rate of reaction and pronounced induction period.

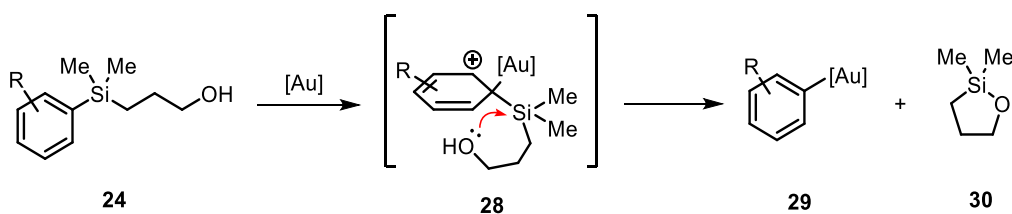


**Scheme 1.12.** Use of an NHC-gold(I) pre-catalyst to facilitate the coupling of heteroarenes.

Lloyd-Jones and co-workers subsequently expanded the substrate scope of the arene coupling partner with the development of bespoke hypervalent iodine(III) and silyl reagents (Scheme 1.13).<sup>52</sup> These facilitated the coupling of more electron rich arenes (including a number of heterocycles) by retarding the formation of diaryliodonium side-products, and accelerating the desired coupling reaction (Scheme 1.14). The alcohol-containing hydroxypropyldimethylsilyl (HPDMS) group allowed the reaction to proceed in the absence of additional methanol, instead generating cyclic siloxane **30** as a by-product.

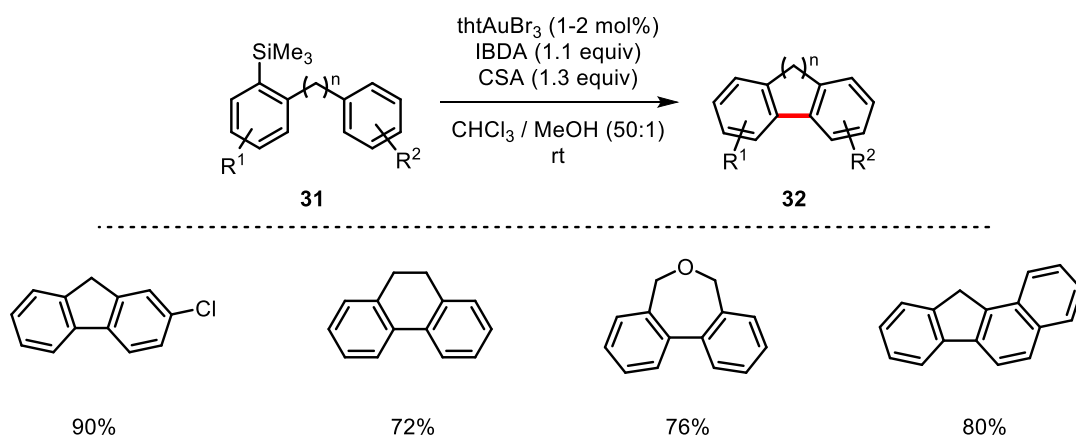


**Scheme 1.13.** HPDMS reagent and bulkier oxidant allow the coupling of various heterocycles.



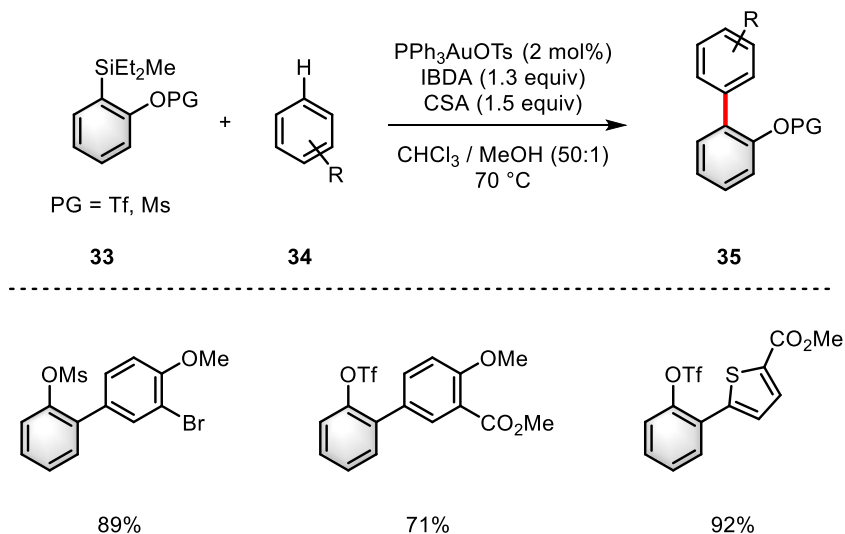
**Scheme 1.14.** Self-cleaving silyl group forming siloxane **30** as a by-product.

The original reaction conditions were later optimised to enable intramolecular coupling, in which the silane and arene components are joined by a tether (Scheme 1.15).<sup>53</sup> Catalyst loadings could typically be reduced to 1 mol% without detriment to the yield, and a range of different ring sizes (5 through to 9) could be formed. Owing to the local proximity of the arene partner in these examples, the reaction is significantly more tolerant of electron-withdrawing substituents. A mechanistic study revealed that, unlike the intermolecular coupling (in which arene  $\pi$ -complexation was turnover limiting), these cyclisation reactions were often governed by the rate of reductive elimination. The reaction (Scheme 1.15) has subsequently been demonstrated to be effective on large-scale and reported in *Organic Syntheses*.<sup>54</sup>



**Scheme 1.15.** Selected examples of the intramolecular arylation reaction to form 5- to 9-membered rings.

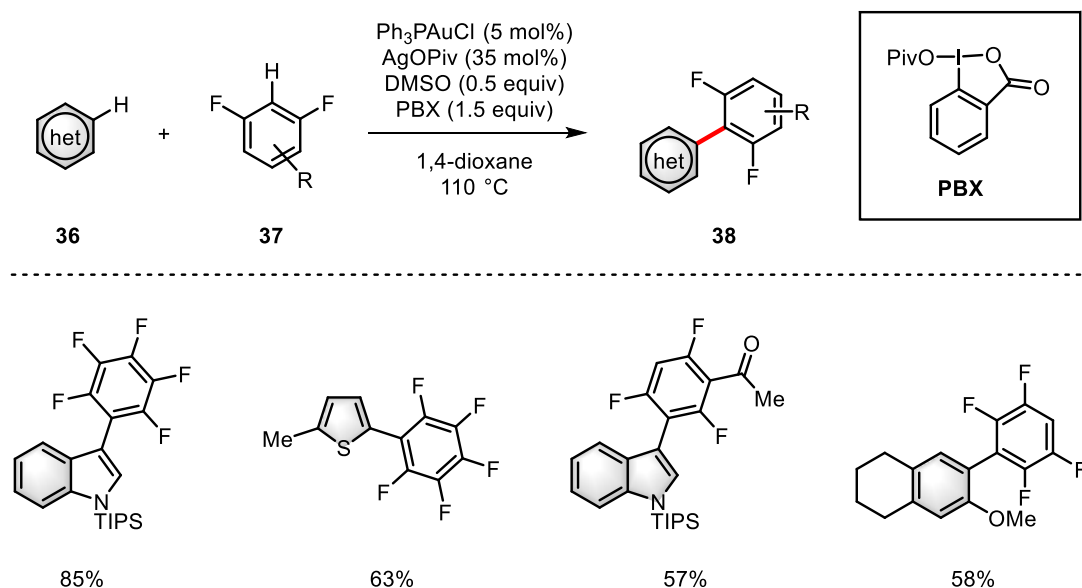
Employing more forcing conditions, Jeon and co-workers were able to couple diethylmethylsilane reagents with a range of arenes (Scheme 1.16).<sup>55</sup> The arylsilane reagents **33**, were accessed *via* a sequential iridium- and rhodium-catalysed C-H silylation of phenol derivatives with  $\text{H}_2\text{SiEt}_2$ . Product yields for the arylation step were generally good and the remaining sulfonate groups could be subjected to Suzuki-Miyaura cross-coupling conditions to synthesise 1,2-triaryls.



**Scheme 1.16.** Coupling of 1,2-silyl phenol derivatives in gold-catalysed direct arylation.

### 1.2.2. Coupling of Electron Deficient Arenes

The contrasting reactivity of gold(I) and gold(III) species was exploited by Larrosa and co-workers in a redox-controlled gold-catalysed dehydrogenative coupling of electron-rich and polyfluorinated (hetero)arenes (Scheme 1.17).<sup>56</sup> A variety of (hetero)arenes can be used as the electron-rich component and the electron poor coupling partner can be modified to some extent (the presence of two *ortho*-fluorine substituents is critical).

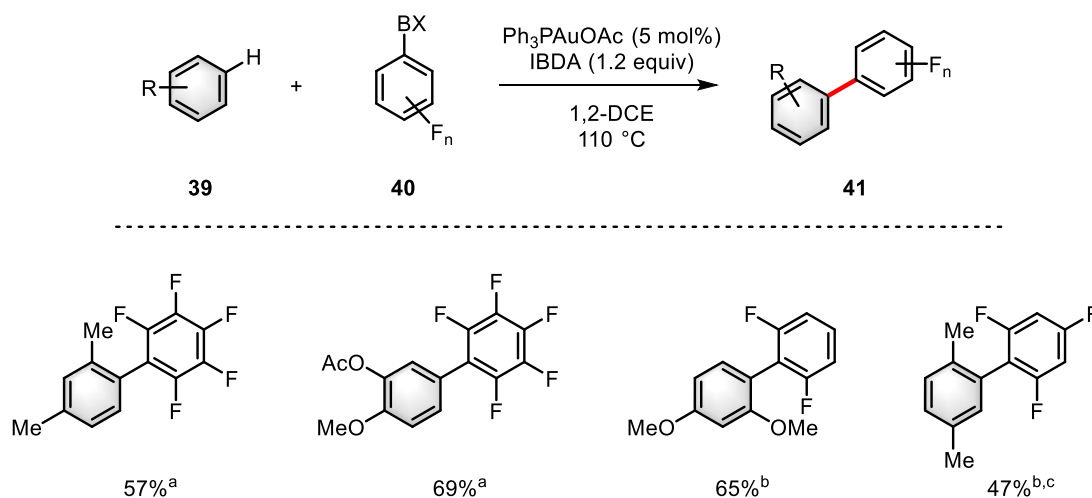


**Scheme 1.17.** Dehydrogenative coupling of electron-rich and electron-deficient arenes, with representative examples.

While the exact reaction mechanism is unclear, the regioselectivity for the electron-rich arene partner is consistent with an electrophilic auration at gold(III). In contrast, the reactive site of the electron-deficient arene is dictated by the most acidic C-H bond, consistent with a concerted metalation-deprotonation (CMD) or deprotonation-metalation mechanism at gold(I).<sup>57–59</sup> The addition of a suitable silver salt ( $\text{AgOPiv}$ ) was found to be essential for catalytic turnover, and its role proven to be more complex than a simple halide extraction (potentially involved in C-H activation of the polyfluorinated arene). Likewise, the role of  $\text{DMSO}$  as an additive was not fully understood, possibly aiding solubility or serving to ligate the catalyst.

The cross-coupling of polyfluorinated organometallic reagents is generally considered to be challenging due to fast competing protodemetalation pathways, particularly under the basic conditions common to most palladium-catalysed cross-couplings.<sup>60–63</sup> To overcome this,

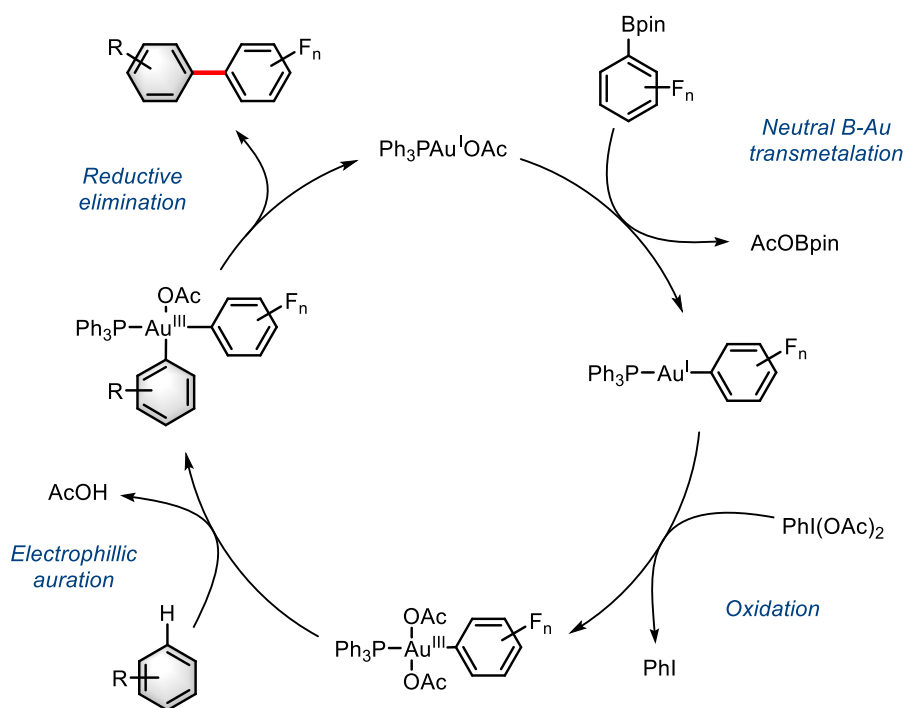
Nevado and co-workers reported a neutral gold-catalysed coupling of electron-rich arenes and polyfluorinated boronic acid derivatives (Scheme 1.18).<sup>64</sup>



**Scheme 1.18.** Gold-catalysed oxidative coupling of polyfluoroboronic acids with arenes.

[a] X = pinacol ester; [b] X = 2,4-pentanediol ester; [c] 10 mol% catalyst.

This methodology again relies on the disparate reactivity of gold(I) and gold(III) species to enable heterocoupling to take place. Unlike traditional palladium cross-coupling, no external base is needed in this case, as the acetate ligand is sufficiently basic to perform the deprotonation. Following a series of stoichiometric studies, a mechanism involving initial transmetalation to gold(I), followed by oxidation, and electrophilic auration was established (Scheme 1.19).

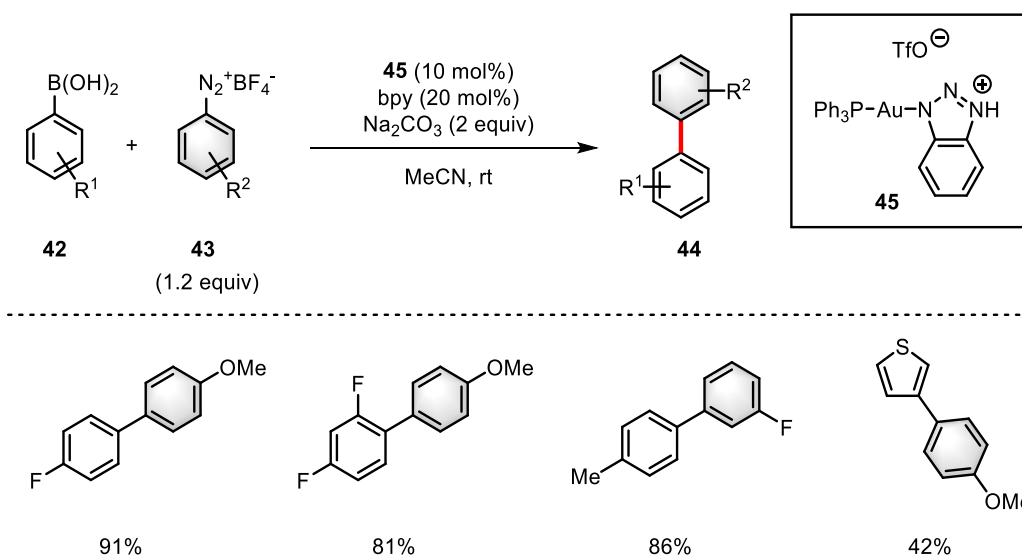


**Scheme 1.19.** Nevado's proposed catalytic cycle for the gold-catalysed arylation of polyfluorinated boronic acid derivatives.

### 1.2.3. Aryldiazonium Salts

In 2015, Shi and co-workers reported the first gold-catalysed coupling of arylboronic acids and aryldiazonium salts to synthesise non-symmetrical biaryls (Scheme 1.20).<sup>65</sup> The aryldiazonium salt serves as both a coupling partner and oxidant, removing the requirement for addition of a strong, sacrificial oxidant, and generating  $N_2(g)$  as a benign by-product.<sup>iv</sup> Cationic triazole-ligated catalyst **45** was found to give reliably higher yields, an outcome attributed to the high stability of the complex.<sup>66</sup>

<sup>iv</sup> Note: Aryldiazonium salts have also been used in gold-catalysed ring expansion<sup>141</sup> and oxyarylation.<sup>142</sup>

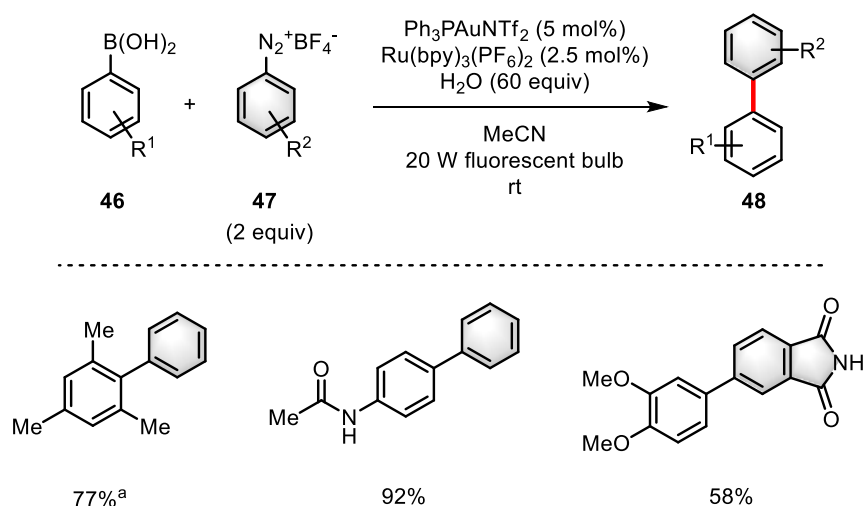


**Scheme 1.20.** Gold-catalysed cross-coupling of arylboronic acids and aryl diazonium salts, with representative examples.

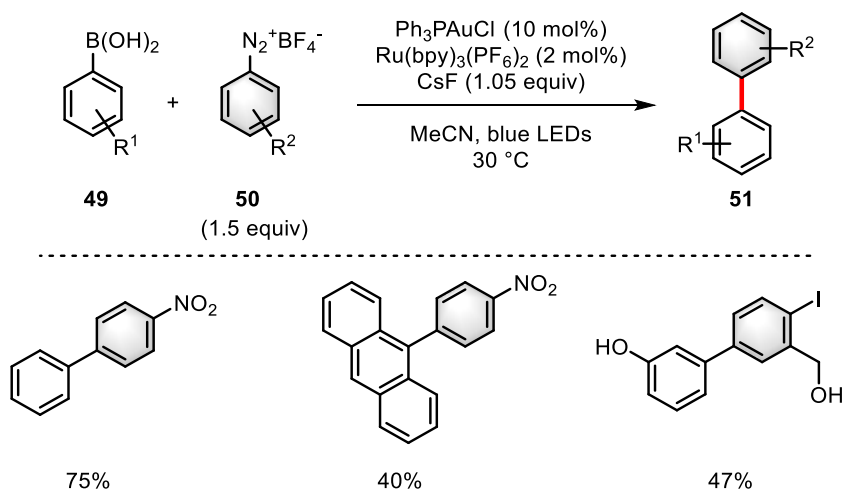
The addition of 2,2'-bipyridine was found to be critical for catalytic turnover, with stoichiometric studies suggesting that it plays an important role in the promotion of  $\text{N}_2$  extrusion. Radical trapping experiments suggested that “free” aryl radicals are not generated under the reaction conditions, instead favouring a simultaneous transmetalation and loss of  $\text{N}_2$ . The boronic acid component could be directly substituted for a terminal alkyne to enable the corresponding alkynylation of various aryl diazonium salts.

The reaction conditions were simultaneously adapted by Lee,<sup>67</sup> Fouquet,<sup>68</sup> and their respective co-workers to invoke a photoredox catalysis manifold (Scheme 1.21 and 1.22).





**Scheme 1.21.** Lee's photoredox modification of the gold-catalysed coupling of aryl diazonium salts.



**Scheme 1.22.** Fouquet's photoredox modification of the gold-catalysed coupling of aryl diazonium salts.

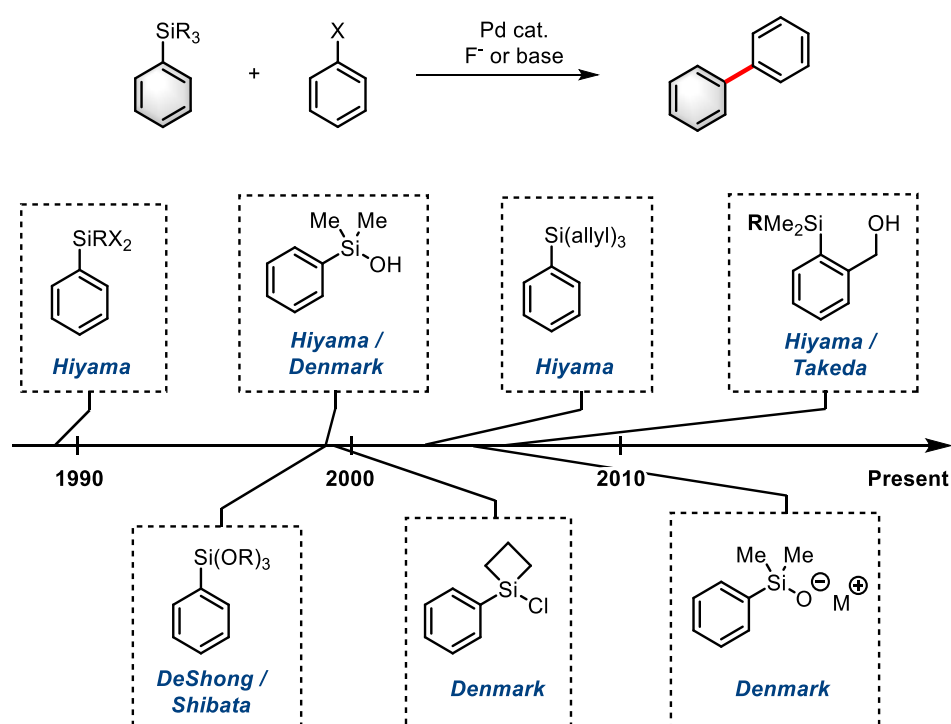
Both protocols exhibit an impressive tolerance for electronically diverse substituents on both aryl partners, as well as some examples of sterically challenging couplings. However, given that there is precedent to suggest that the reaction can proceed in the absence of photocatalyst,<sup>65,68</sup> care must be taken when considering if the reaction mechanisms are truly operating under a photoredox catalysis cycle (or simply photoinitiated).<sup>69</sup>

### 1.3. Arylsilanes in Transition Metal Catalysis

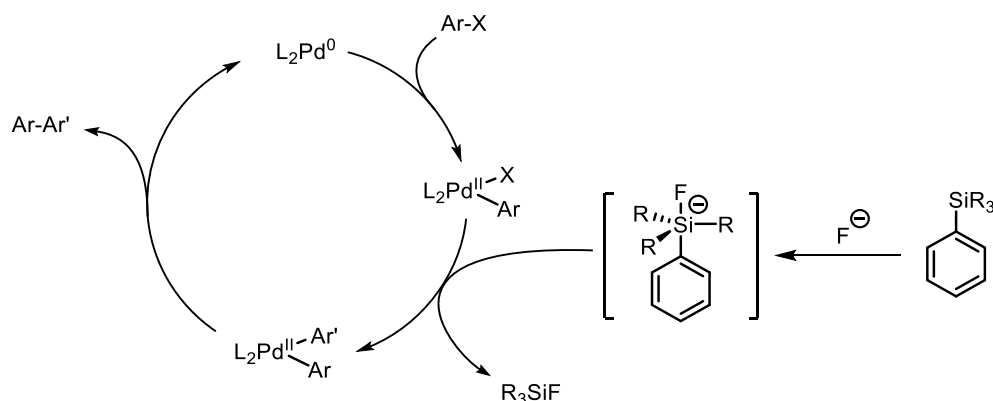
Organometallic reagents derived from tin, zinc, and boron have found widespread application in transition metal catalysis, particularly in the field of palladium cross-coupling, due to their broad functional group compatibility.<sup>70–72</sup> Organosilicon compounds, while less commonly encountered, represent an attractive alternative owing to their comparably low toxicity, high stability, and ease of handling.<sup>73</sup>

#### 1.3.1. Palladium-Catalysed Hiyama-Denmark Coupling

Hiyama and co-workers first demonstrated the potential for organosilanes to be used as organometallic reagents in the synthesis of biaryls almost 30 years ago (Figure 1.3).<sup>74,75</sup> Aryl(dihalo)silanes could be activated toward transmetalation to palladium using a superstoichiometric quantity of a fluoride source, and reacted with aryl halides to afford non-symmetrical biaryls.<sup>76–78</sup> It is proposed that the reaction proceeds *via* formation of a pentavalent silicon species, which is required to facilitate transmetalation to the palladium catalyst (Scheme 1.23).



**Figure 1.3.** Timeline of developments in arylsilane reagents for use in Hiyama-Denmark cross-coupling.



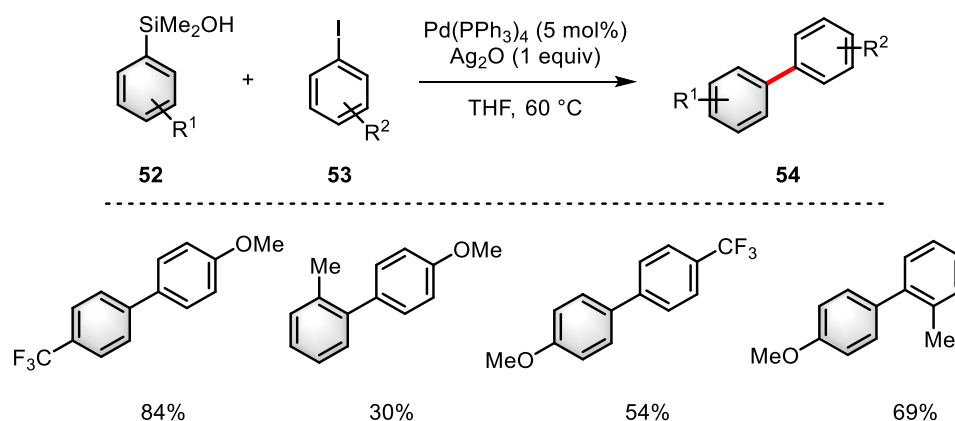
**Scheme 1.23.** General catalytic cycle for fluoride-activated Hiyama coupling.

DeShong, Shibata, and co-workers demonstrated that it was possible to replace the moisture-sensitive (dihalo)silanes with more robust trialkoxysilane<sup>v</sup> reagents.<sup>79–83</sup> Shortly after this, Hiyama and co-workers reported that triallyl silanes could be used, offering improved product yields, while still exhibiting stability toward moisture, acids, and bases.<sup>84–86</sup> All of these methods however, are restrictive in their requirement for a superstoichiometric fluoride source, limiting their appeal to the broader synthetic community; many natural product syntheses rely on the use of silyl protecting groups, which are readily cleaved in the presence of fluoride sources.<sup>87,88</sup>

The earliest demonstrated use of arylsilanols in a palladium-catalysed cross-coupling with aryl iodides was reported by Hiyama and co-workers in 1999 (Scheme 1.24).<sup>89,90</sup> Ag<sub>2</sub>O was required as a stoichiometric activator, likely serving the dual purpose of catalyst activation (through iodide abstraction) and facilitating transmetalation of the arylsilanol. While advantageous in that a fluoride activator was not necessary, reaction times were often protracted.<sup>vi</sup>

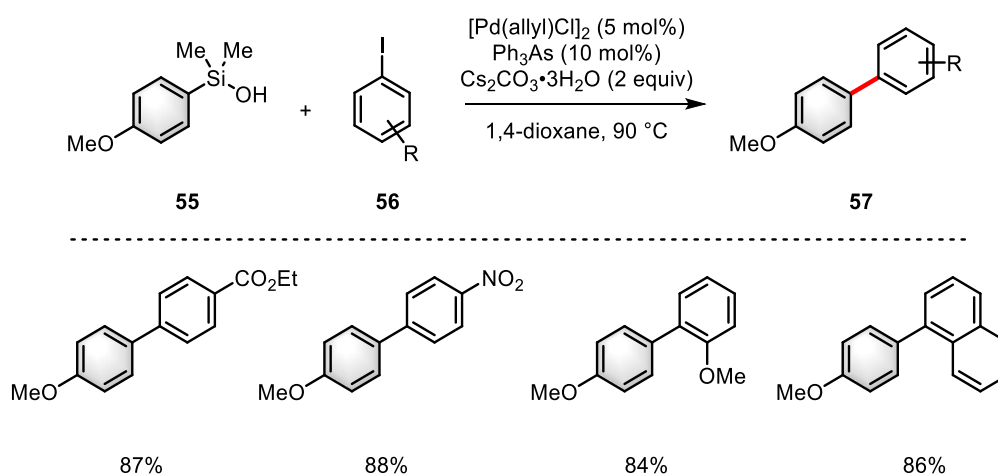
<sup>v</sup> Alkenylalkoxysilanes had previously been used in palladium-catalysed couplings by Tamao and Ito.<sup>143</sup>

<sup>vi</sup> Denmark and co-workers reported the use of aryl(halo)silanes in cross-coupling. However, it was later discovered that the TBAF activator simply led to cleavage of the silane and the *in situ* formation of silanols.<sup>144,145</sup>

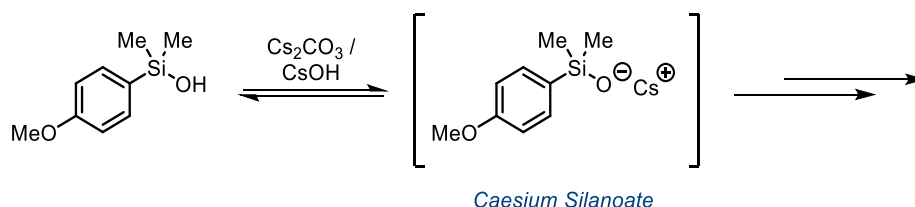


**Scheme 1.24.** Hiyama coupling of arylsilanols using silver(I) oxide as an additive.

Alternatively, the reaction can be promoted by cesium-containing bases, typically carbonate or hydroxide (Scheme 1.25).<sup>91,92</sup> However, it is essential in this case that the salts are used as hydrates, as the water ensures that formation of inactive disiloxane by-products is reversible. Under these Brønsted base-activated conditions, the deprotonated silanol (silanoate) is formed *in situ*, and is likely the species responsible for transmetalation (Scheme 1.26). Depending on the base strength, this silanoate formation may or may not be quantitative under the reaction conditions. The use of strong alkoxide base helps to ensure that complete deprotonation occurs, but limits the compatibility with various functional groups.

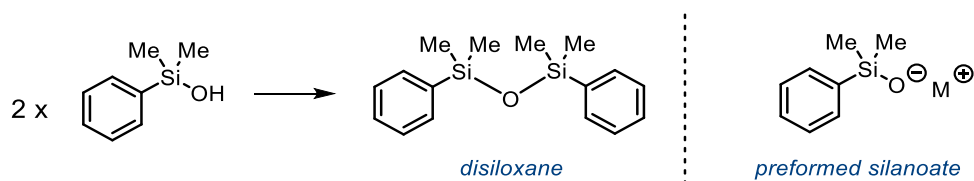


**Scheme 1.25.** Denmark's coupling of arylsilanols using cesium-containing bases.



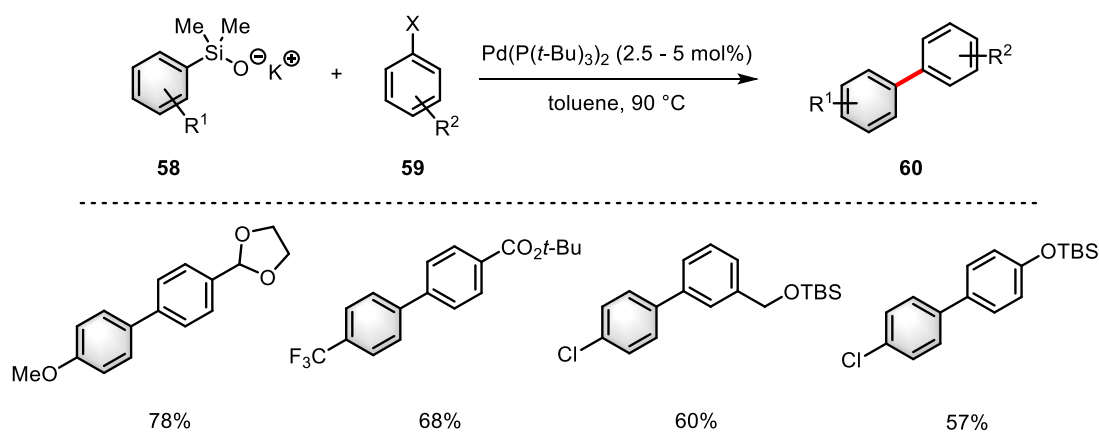
**Scheme 1.26.** In situ formation of a caesium silanoate, the species likely involved in transmetalation.

The problematic dimerisation of silanols to form disiloxanes can be avoided if the preformed metal silanoates are prepared and used instead (Scheme 1.27). This can be achieved in a one-pot stepwise manner, using a strong base (such as a metal hydride) to ensure quantitative deprotonation,<sup>93,94</sup> or alternatively the metal silanoate salt can be prepared and isolated prior to use. Championed by Denmark and co-workers, these conjugate bases of the free silanols are typically stable, free-flowing powders, that can be used directly without the need for any additional activators.<sup>95,96</sup>

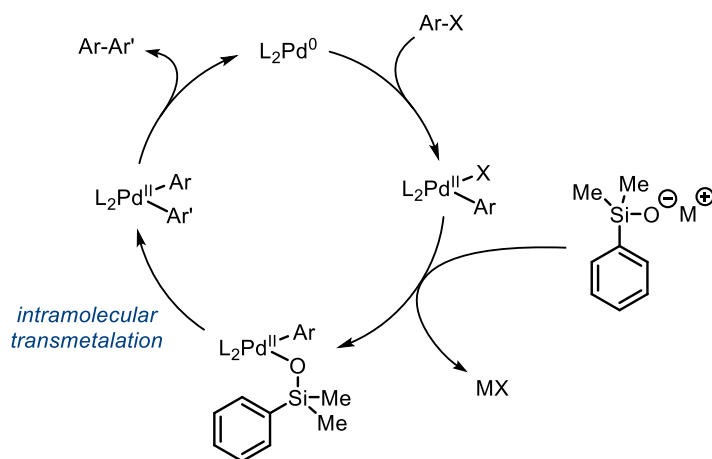


**Scheme 1.27.** Problematic disiloxane formation (left) and isolated silanoate (right) to avoid dimerization.

Using potassium arylsilanoates in the presence of a  $\text{Pd}(\text{P}(t\text{-Bu})_3)_2$  catalyst, Denmark and co-workers were able to cross-couple an impressive range of aryl chlorides and bromides (Scheme 1.28).<sup>97</sup> Yields were typically high, and sensitive functional groups (esters, cyclic acetals, TBS-protected alcohols) as well as various heterocycles were well tolerated. The choice of catalyst and ligand proved vital for effective coupling, with other combinations resulting in limited reactivity.<sup>98</sup> Mechanistic studies support a general catalytic cycle involving initial coordination of the silanoate to the metal centre, before an external base-free transmetalation to deliver the aryl group (Scheme 1.29).

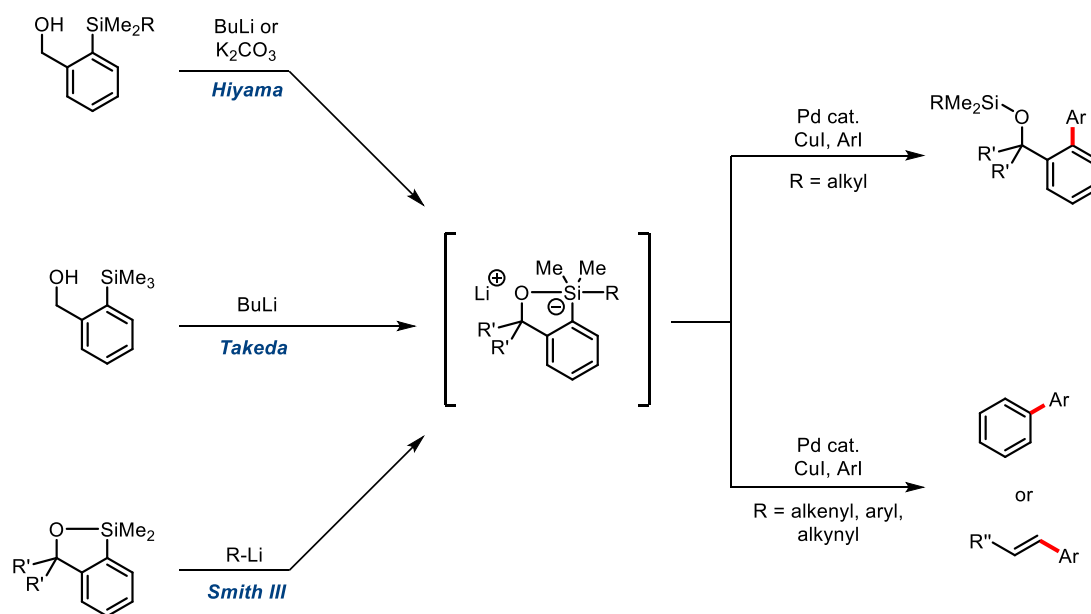


**Scheme 1.28.** Denmark's external base-free coupling of metal silanoates and aryl halides.



**Scheme 1.29.** Proposed mechanism for Hiyama-Denmark cross-coupling reactions involving preformed arylsilanoates.

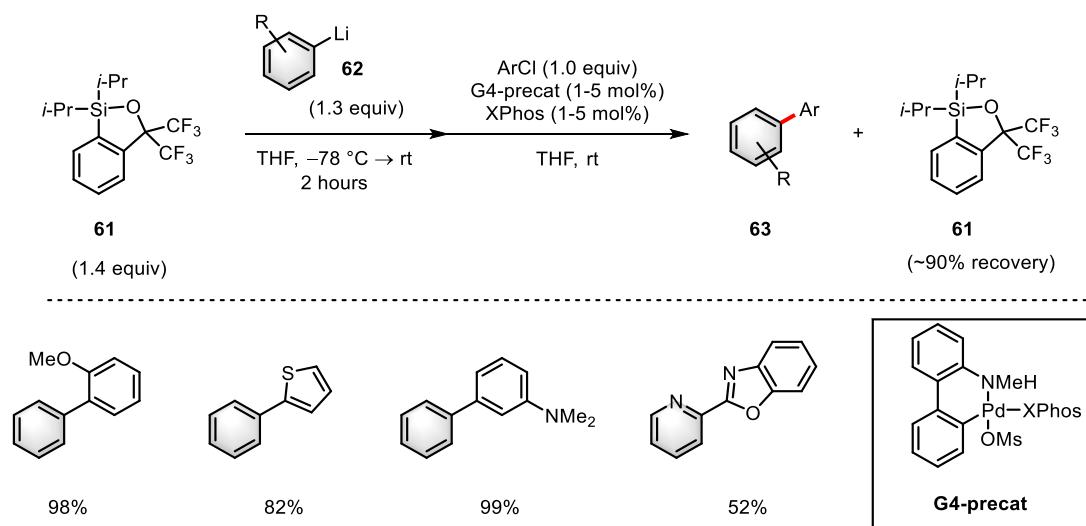
In 2005, Hiyama and co-workers reported the use of a modified silyl reagent that incorporated a pendant alcohol on the arene (Scheme 1.30). Termed HOMSi reagents, they undergo *in situ* deprotonation to form pentavalent silicate species that are capable of transferring aryl, alkenyl, and alkynyl groups in metal-catalysed reactions.<sup>99-102</sup> Depending on the nature of the substituents at silicon, the reagent can either act as a transfer reagent (Hiyama pathway) or as a direct cross-coupling partner (Takeda pathway).<sup>103</sup>



**Scheme 1.30.** Different pathways for HOMSi reagent activation and reactivity.<sup>vii</sup>

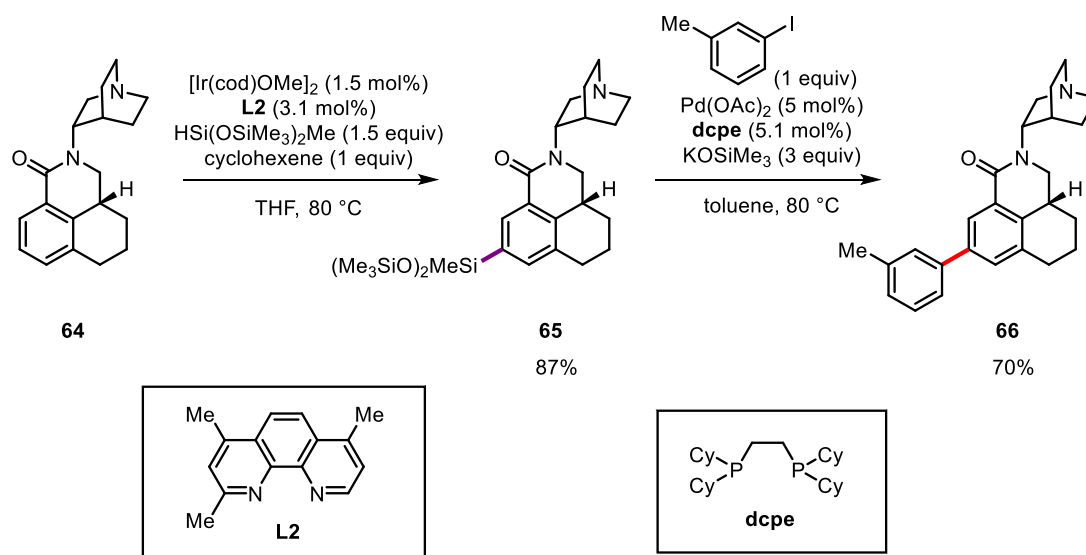
The same intermediates have more recently been utilised by Smith III and co-workers in a formal palladium-catalysed coupling of organolithium reagents, which represents an alternative to existing Murahashi<sup>104,105</sup> and Feringa<sup>106–108</sup> couplings (Scheme 1.30). The 1-oxa-2-silacyclopentene transfer reagents are regenerated following transmetalation, and can therefore be easily recovered and reused.<sup>109–113</sup> Rational modification of the transfer reagent has enabled the more challenging cross-coupling of aryl chlorides at room temperature (Scheme 1.31).

<sup>vii</sup> A similar siloxane transfer reagent was independently reported by Tamao and co-workers.<sup>146</sup>



**Scheme 1.31.** Cross-coupling of organolithium compounds using an arylsilane transfer reagent.

Hartwig and co-workers reported a dehydrogenative silylation of arenes (catalysed by either rhodium or iridium) followed by cross coupling in the presence of a palladium catalyst to form biaryls, as well as other functionalised products (Scheme 1.32).<sup>114–117</sup> The regioselectivity of the silylation is largely governed by steric effects, and the reaction conditions are tolerant of an impressive range of functional groups. This was showcased in the silylation of a range of natural products, offering a convenient method for the late-stage functionalisation of highly complex molecules.



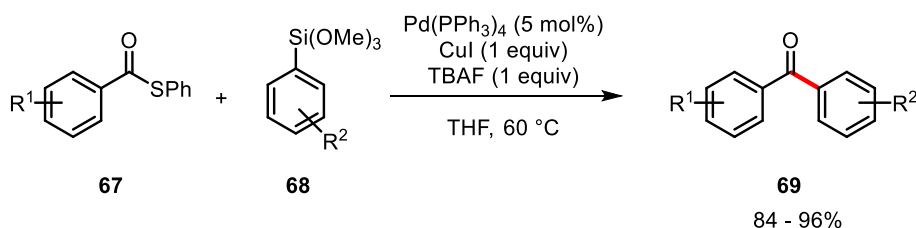
**Scheme 1.32.** Hartwig's silylation-arylation sequence for late-stage functionalisation.



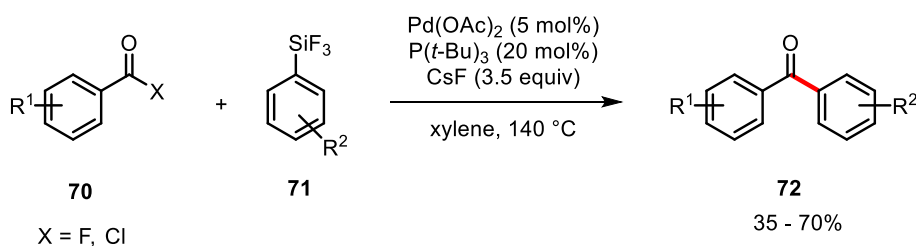
### 1.3.2. Other Palladium-Catalysed Reactions of Arylsilanes

Similar conditions to those required for Hiyama coupling can also promote the synthesis of diarylketones. Van der Eycken and co-workers reported the desulfitative coupling of arylthioesters with arylsiloxanes, to generate the corresponding diarylketones in good yield (Scheme 1.33).<sup>118</sup> More recently, Sakai and co-workers have shown that the analogous reaction using acyl chlorides (or fluorides) is also possible.<sup>119</sup> Alternatively, the polarity of the coupling partners can be reversed in the coupling of aryl halides and acylsilanes, as demonstrated by Krska and co-workers.<sup>120</sup>

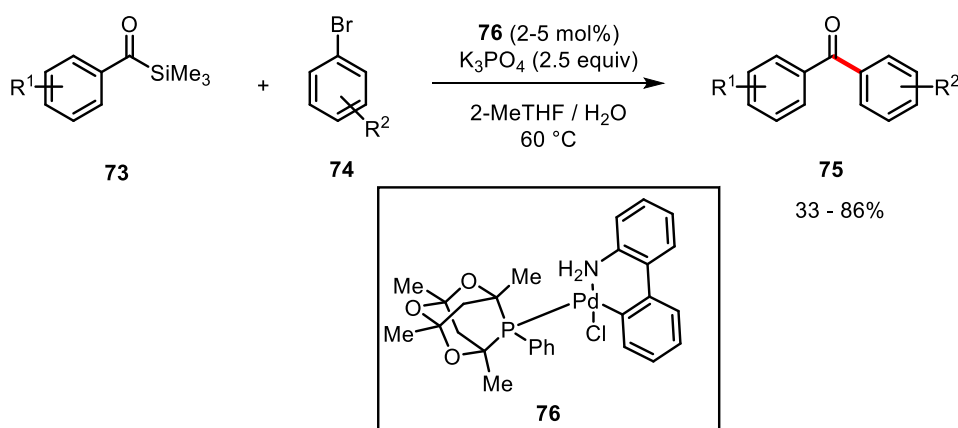
#### Van der Eycken (2008)



#### Sakai (2016)

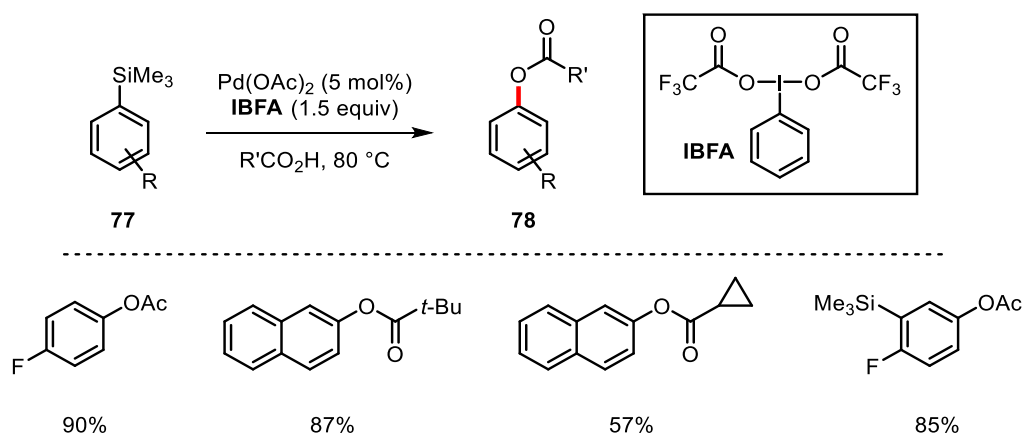


#### Krska (2011)



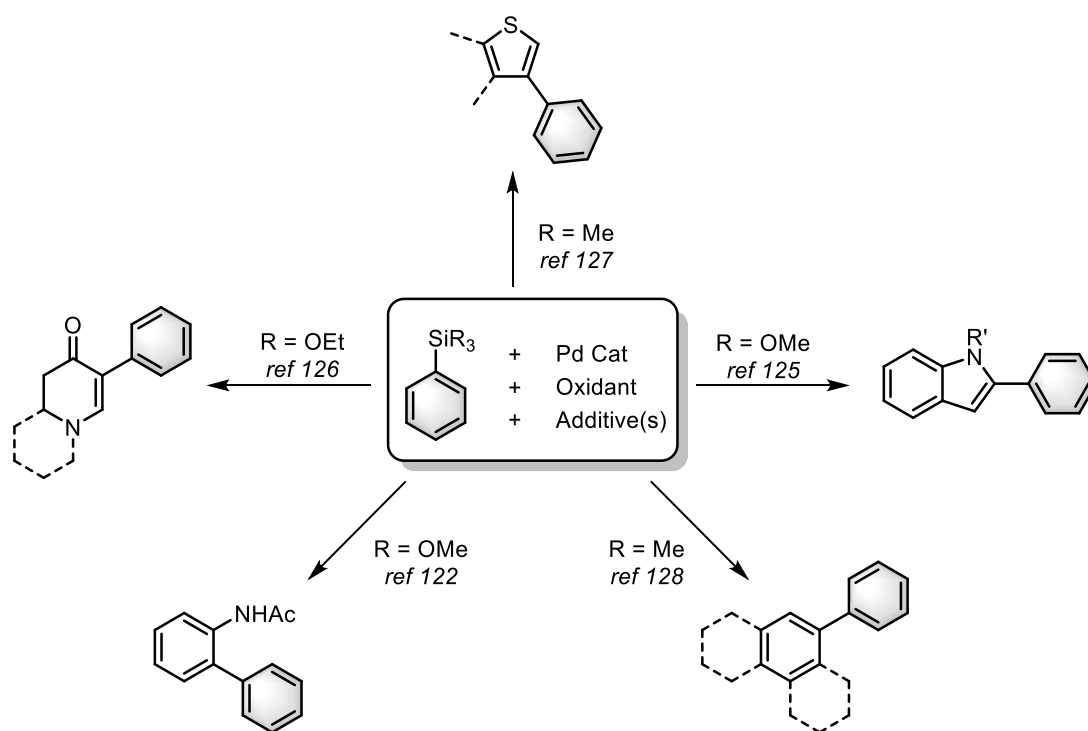
**Scheme 1.33.** Summary of palladium-catalysed methods to synthesise diarylketones from arylsilanes.

Kitamura and co-workers reported an oxidative palladium-catalysed acetoxylation of arylsilanes using PIFA as a terminal oxidant in AcOH at 80 °C (Scheme 1.34).<sup>121</sup> The acetoxyarenes are obtained in good yield, and both electron-rich and electron-poor arylsilanes are compatible. Performing the reaction in alternative carboxylic acid solvents leads to formation of the corresponding esters. The mechanism is suggested to proceed via a palladium(II/IV) redox cycle, though experimental evidence in support of this is lacking.



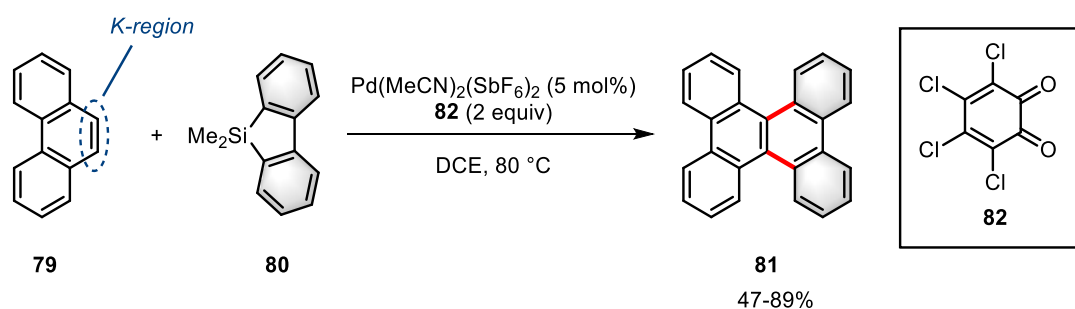
**Scheme 1.34.** Kitamura's palladium-catalysed carboxylation of arylsilanes.

A variety of oxidative palladium-catalysed C-H activation reactions employing arylsilanes are possible (Scheme 1.35).<sup>122–128</sup> Copper salts are typically added as an external oxidant, and in most cases a fluoride source is required to activate the arylsilane to transmetalation.



**Scheme 1.35.** Overview of C-H functionalisation reactions involving arylsilanes.<sup>viii</sup>

Interestingly, Itami and co-workers were able to use cationic palladium catalyst  $\text{Pd}(\text{MeCN})_4(\text{SbF}_6)_2$  in the K-region selective arylation of pyrenes, without the need for any additional fluoride additive (Scheme 1.36).<sup>129</sup> Parallels can be drawn between this reaction and gold-catalysed arylation, in which the presence of a highly electrophilic catalyst allows the transmetalation of non-activated, neutral aryltrimethylsilanes.

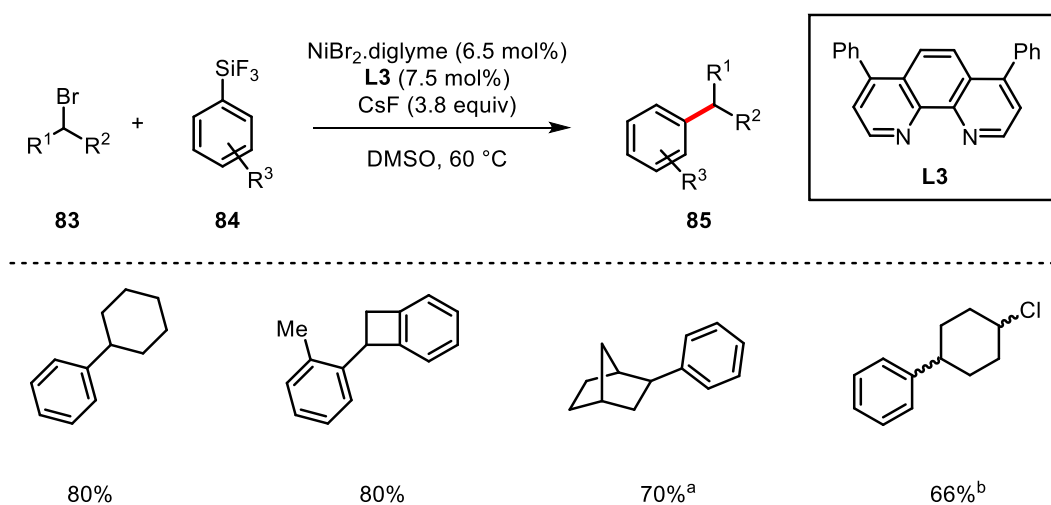


**Scheme 1.36.** Itami's fluoride-free palladium-catalysed annulation reaction using arylsilane **80**.

<sup>viii</sup> A select number of nickel-<sup>147</sup> and rhodium-<sup>148</sup> catalysed C-H functionalisations using arylsilane reagents have also been reported.

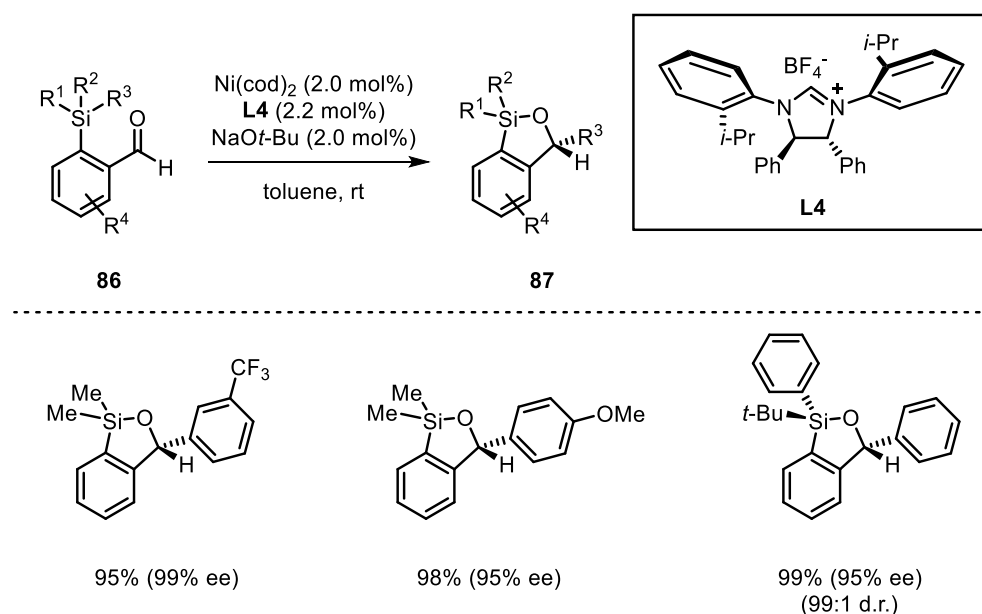
### 1.3.3. Nickel-Catalysed Reactions of Arylsilanes

In addition to palladium, a range of transformations utilising arylsilane reagents can be carried out in the presence of a nickel catalyst. For example, a nickel-phenanthrene complex was shown by Fu and co-workers to promote the coupling of aryl(trifluoro)silanes with secondary alkyl bromides (Scheme 1.37).<sup>130</sup> The reaction exhibits reasonable functional group tolerance and can also be applied to a select number of primary alkyl halides. The stereochemical outcome of some couplings suggest that the mechanism may be radical in nature, though current experimental evidence is inconclusive.



**Scheme 1.37.** Fu's nickel-catalysed alkylation of arylsilanes. [a] 95:5 exo/endo (starting material 6:94); [b] 55:45 cis/trans (starting material 95:5).

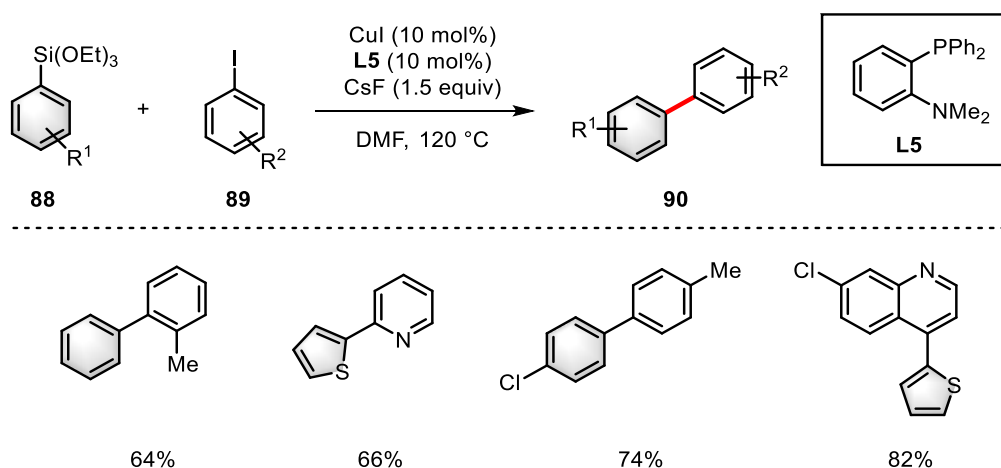
Ogoshi and co-workers reported the use of a chiral nickel NHC complex to effect an intramolecular asymmetric addition of arylsilanes across aldehydes (Scheme 1.38).<sup>131,132</sup> The method is high yielding and the resulting products are generated with excellent control over enantioselectivity. Using diphenylarylsilane reagents as precursors allows two quaternary stereocentres to be formed in one transformation (one at silicon and one at carbon).



**Scheme 1.38.** Ogoshi's asymmetric nickel-catalysed intramolecular addition into aldehydes.

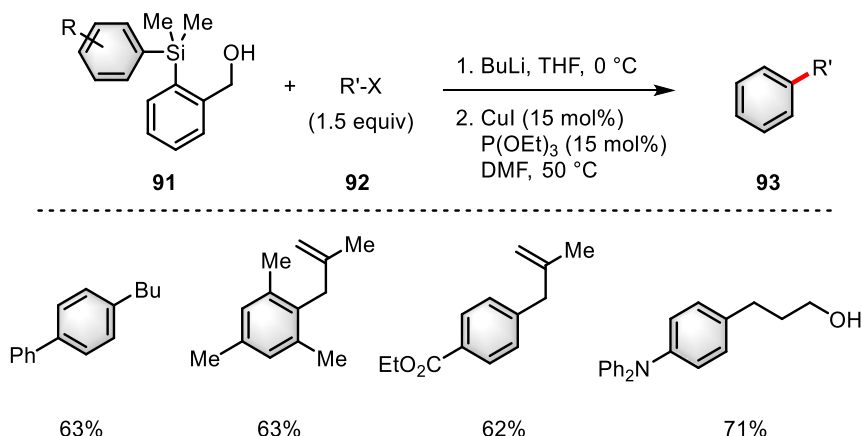
### 1.3.4. Copper-Catalysed Reactions of Arylsilanes

While copper has often been used as a co-catalyst or additive in palladium-catalysed reactions of organosilanes, there are some notable examples in which a copper species is able to act as the sole catalyst. Giri and co-workers described a copper-catalysed cross-coupling of arylsiloxanes with (hetero)aryl iodides (Scheme 1.39).<sup>133,134</sup> Product yields for most couplings were found to be reliably higher when using bidentate P,N-ligand **L5**, though nitrogen-containing heteroarenes underwent more efficient coupling in the absence of any additional ligand. It is proposed that both the ligand and CsF help to prevent the formation of (aryl)copper aggregates, which are the assumed primary pathway for homocoupling by-products.



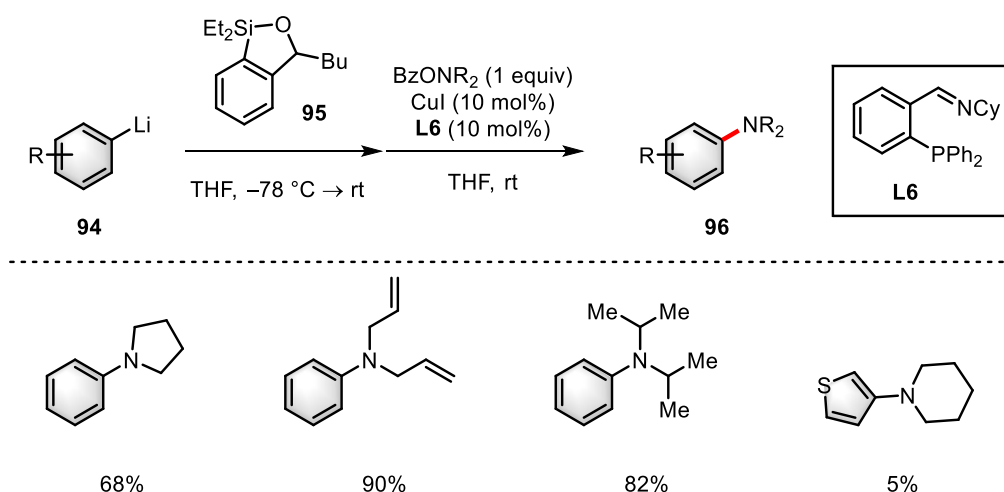
**Scheme 1.39.** Copper-catalysed cross-coupling of (hetero)arylsiloxanes and (hetero)aryl iodides.

Similarly, Takeda and co-workers demonstrated that aryl HOMSi reagents could be used in the presence of a copper catalyst to enable the alkylation of arenes (Scheme 1.40).<sup>135</sup> Primary alkyl iodides, as well as allyl/benzyl chlorides can be used as the alkyl donor, and a number of different arenes were shown to be effective. Notably, free alcohols could be tolerated without significant detriment to the product yield.

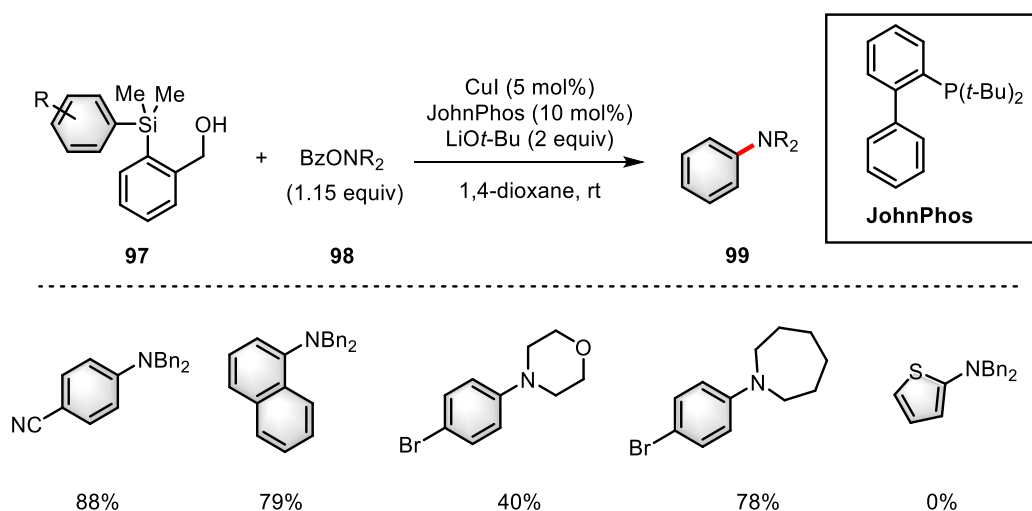


**Scheme 1.40.** Copper-catalysed alkylation of aryl HOMSi reagents.

Aryl HOMSi reagents could also be used to facilitate a copper-catalysed electrophilic amination independently reported by Smith III,<sup>112</sup> and Hirano, Miura and co-workers (Scheme 1.41 and 1.42).<sup>136</sup> Both methods exhibit a reasonably broad substrate scope, though thiophene-derived or sterically hindered arenes proved ineffective (in contrast to other HOMSi related reactions).



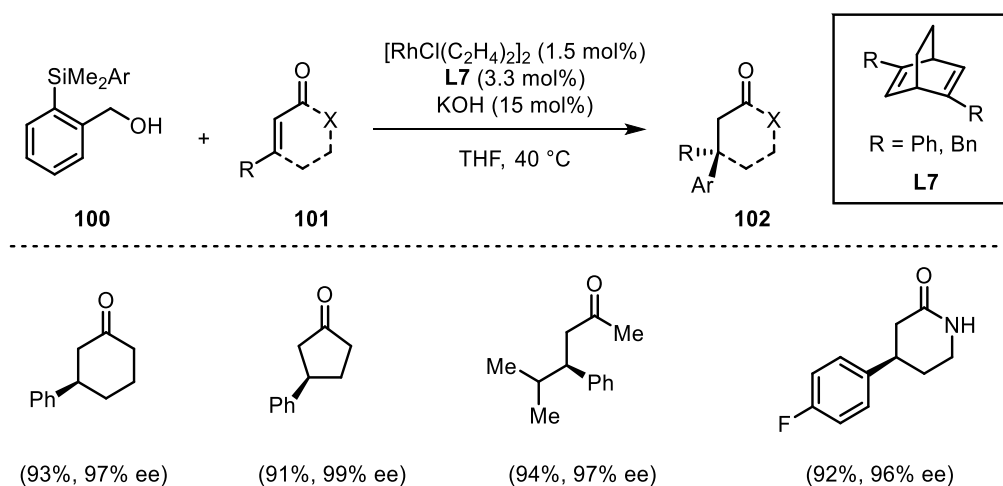
**Scheme 1.41.** Smith III method for electrophilic amination using HOMSi reagents.



**Scheme 1.42.** Hirano and Miura method for electrophilic amination using HOMSi reagents.

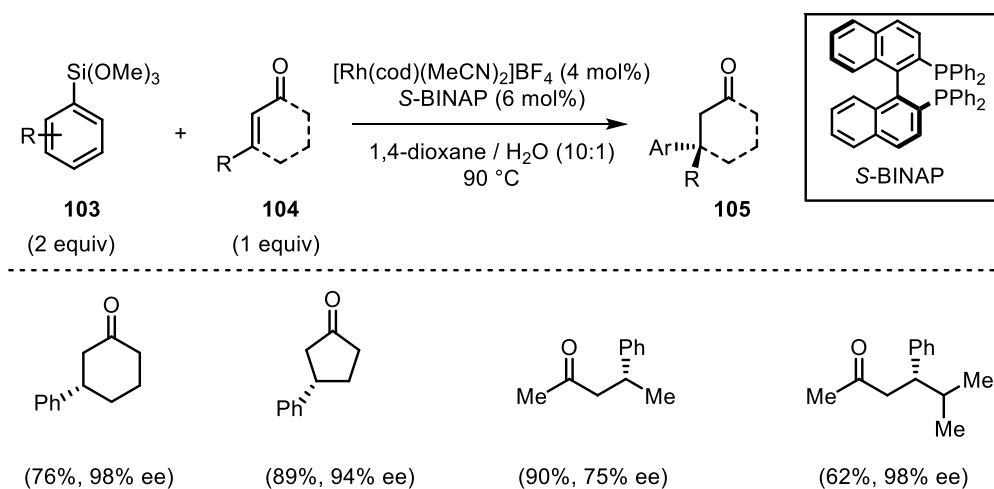
### 1.3.5. Rhodium-Catalysed Reactions of Arylsilanes

A variety of rhodium catalysts have been used to enable enantioselective 1,4-additions of arylsilanes to  $\alpha,\beta$ -unsaturated carbonyl compounds. Hiyama and co-workers reported that aryl HOMSi reagents can undergo transmetalation with a rhodium hydroxide derived catalyst in the presence of a catalytic amount of  $\text{KOH}$ , under mild conditions ( $40\text{ }^{\circ}\text{C}$ , THF), to enable conjugate additions with a range of Michael acceptors (Scheme 1.43).<sup>137</sup> Chiral dienes (of the general structure **L7**) were used to render the reaction asymmetric, resulting in reliably high product yields and enantioselectivities.



**Scheme 1.43.** Hiyama's asymmetric rhodium-catalysed conjugate addition reaction using HOMSi reagents.

Oi and co-workers independently reported that trialkoxyarylsilanes could also be used in the presence of an (*S*)-BINAP ligated rhodium catalyst to enable conjugate addition into α,β-unsaturated ketones (Scheme 1.44).<sup>138</sup> The level of enantiocontrol is similar to the Hiyama method despite the more forcing reaction conditions. In this instance, with a cationic rhodium species, it was found that no external base was needed to activate the arylsilane reagent.



**Scheme 1.44.** Oi's asymmetric rhodium-catalysed conjugate addition into α,β-unsaturated ketones.



## 1.4. Summary

Despite the emergence of arylsilicon reagents as a viable alternative to established organometallic reagents for a variety of cross-coupling reactions, they remain largely underutilised by the broader synthetic community. This is in part due to the common requirement for a superstoichiometric (often fluoride-containing) activating agent to enable the silyl reagent to undergo transmetalation with a transition metal catalyst. Gold(III) catalysis offers a convenient solution to this issue, with the highly electrophilic nature of the catalyst facilitating an additive-free transmetalation (using simple trialkylarylsilanes).

While oxidative gold catalysis has emerged as a powerful synthetic tool to form C–C bonds, key information regarding the reaction mechanism under operation is often lacking. It is broadly appreciated that a better understanding of the fundamental mechanistic limitations of the chemistry will aid the design and development of future methodologies.

The work detailed in this thesis summarises our investigation into a class of unreactive arylsilane reagents, and the subsequent development of a method to enable them to be used as coupling reagents in gold catalysis. We anticipate that the findings will be of interest not only within the remit of direct arylation, but perhaps also to the wider community of late transition metal catalysis.

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**Transmetalation of *ortho*-Substituted Arylsilanes in  
Gold Catalysis**

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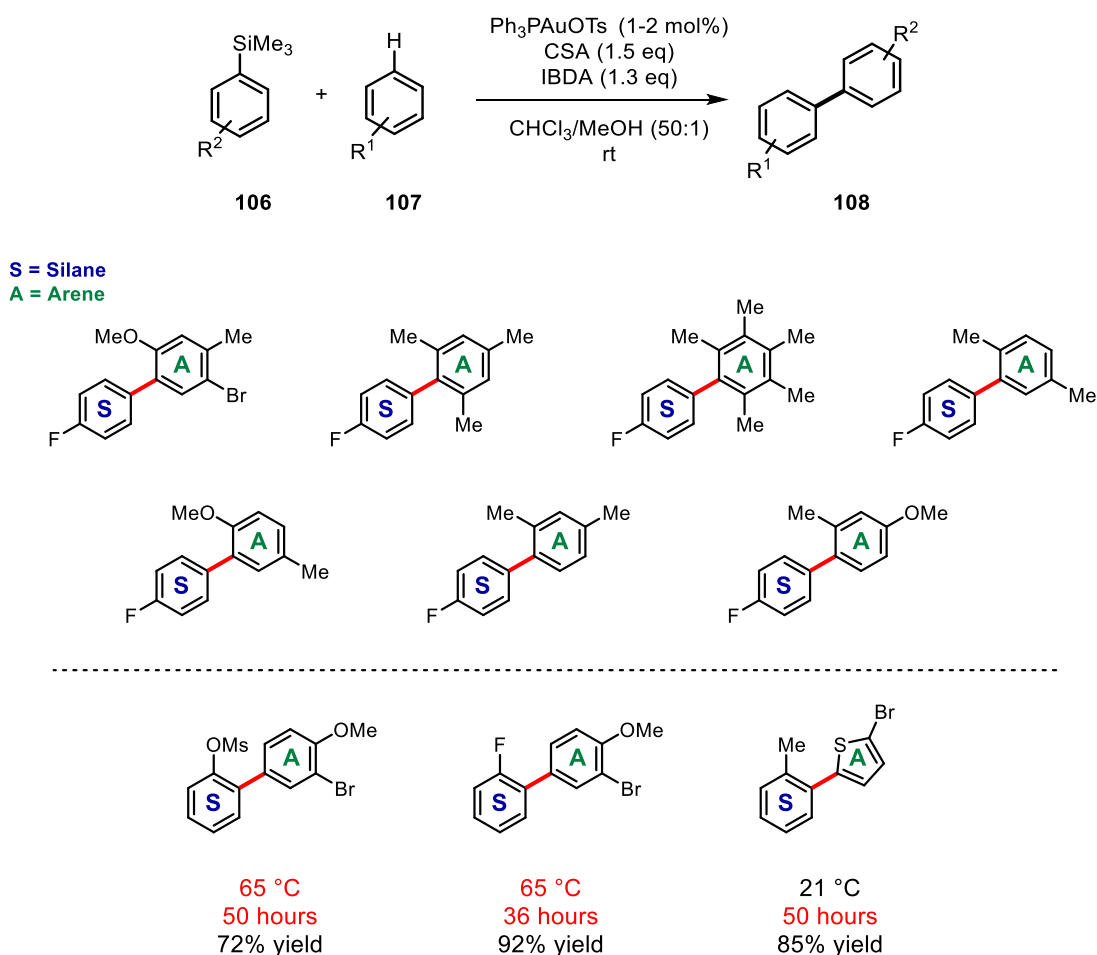
## 2.1 Introduction

### 2.1.1 Limitations in Gold-Catalysed Direct Arylation

The complexity of target molecules throughout industrial chemistry is driving the development of synthetic methods that are tolerable of a wide variety of different functional groups. Likewise, methods for the late-stage incorporation of structural and electronic diversity are highly desirable in compound library syntheses, placing a great deal of importance on the generality of synthetic procedures.

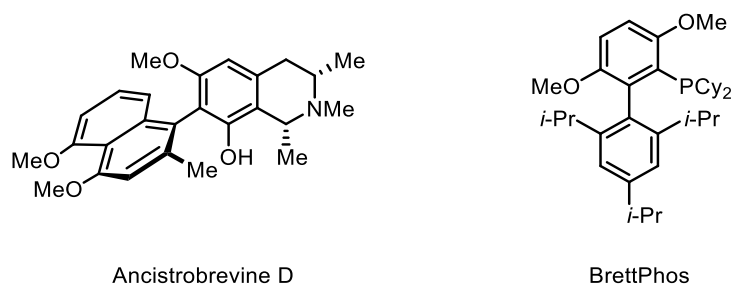
One of the key strengths of the gold-catalysed arylation reaction in this respect is versatility with regard to the coupling partners. A range of  $\pi$ -rich (hetero)arenes are suitable, along with an electronically diverse range of aryltrimethylsilanes.<sup>1,2</sup> The fact that aryl halides, along with selected boronic acid derivatives, are tolerated under the reaction conditions provides an orthogonal reactivity to established transition metal-catalysed cross-coupling. Given the number of commercial syntheses involving palladium-catalysed reactions,<sup>3</sup> this can be expected to offer a broadly practical advantage with respect to the synthetic planning of multi-step sequences.

Despite the substrate scope in previous studies having been demonstrated to be reasonably broad, only select examples exist for the intermolecular coupling of *ortho*-substituted arylsilanes, typically requiring elevated temperatures and/or prolonged reaction times in order to reach reasonable conversion. Indeed, nearly all examples of products that possess substitution at the *ortho*-position are derived from the arene coupling partner rather than the arylsilane (Scheme 2.1). It is unclear at which step the catalytic cycle is adversely affected by *ortho*-substitution of the arylsilane, with transmetalation, C-H auration and reductive elimination all viable possibilities.



**Scheme 2.1.** Products of cross-coupling that have substituents adjacent to the site of arylation.<sup>1</sup>

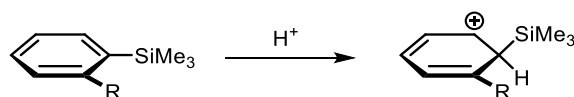
While presently inaccessible *via* gold-catalysed arylation, sterically congested biaryls are an attractive synthetic target due to their prevalence in natural products<sup>4</sup> and ligand structures<sup>5,6</sup> (Figure 2.1). Sufficient substitution on both coupling partners can render the products of cross-coupling axially chiral, with a range of associated properties and applications (See Section 3.5.3).



**Figure 2.1.** Axially chiral natural product, Ancistrobrevine D, and biarylphosphine ligand, BrettPhos.

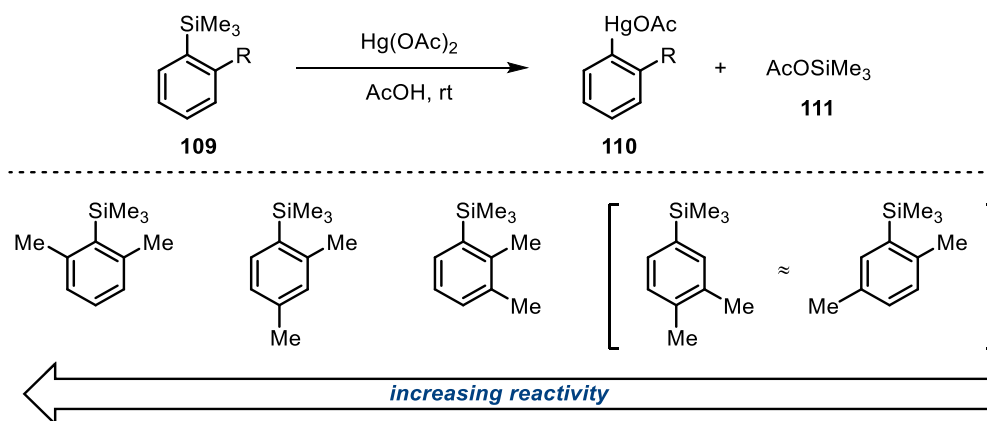
### 2.1.2 *Ortho*-Substituted Arylsilanes in $S_EAr$ Chemistry

The somewhat unusual reactivity of *ortho*-substituted arylsilanes has been noted in a number of electrophilic aromatic substitution ( $S_EAr$ ) reactions. In protodesilylation for example, 2,6-dimethyl-<sup>7</sup> and 2-trimethylsilyl-<sup>8</sup> substituents were found to be significantly more reactive than would be expected based on inductive effects alone. This is attributed to the alleviation of steric strain upon moving from the planar conformation of the ground state toward the *pseudo*-tetrahedral geometry of the Wheland intermediate (Scheme 2.2). Other *ortho*-substituents however, were found to have a minimal steric contribution to the rate of protodesilylation, resulting in a strong correlation between the relative rates of *para*- and *ortho*-substituents.<sup>8</sup>



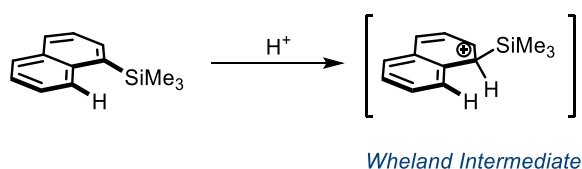
**Scheme 2.2.** Relief of steric strain en route to the Wheland Intermediate for *ortho*-substituted aryltrimethylsilanes.

Similarly, Benkeser and co-workers found that the rate of mercuridesilylation was significantly accelerated for 2,6-dimethyl-substituted arylsilanes, as evidenced by the order of reactivity of the trimethylsilylxylenes (Scheme 2.3).<sup>9</sup> In fact, such was the increase in reactivity, the kinetics of mercuridesilylation for the most reactive silane proved too fast to monitor.



**Scheme 2.3.** Order of reactivity of trimethylsilylxylenes in mercuridesilylation by  $\text{Hg(OAc)}_2$ .

The desilylation of trimethylsilylnaphthalene is significantly faster for the 1-substituted isomer compared to the 2-substituted isomer.<sup>10</sup> This is attributed to an analogous case of steric relief whereby the trimethylsilyl-substituent moves out of plane of the *peri*-hydrogen atom en route to Wheland intermediate formation (Scheme 2.4).

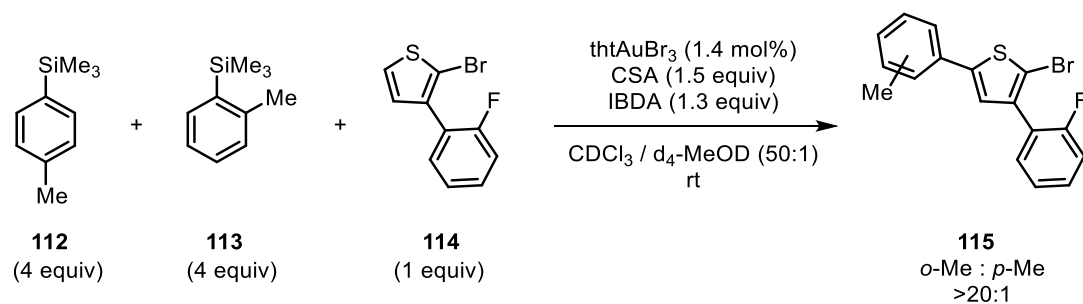


**Scheme 2.4.** Relief of steric strain upon Wheland Intermediate formation for the  $\alpha$ -isomer of (trimethylsilyl)naphthalene.

### 2.1.3 *Ortho*-Substituted Arylsilanes in Gold-Catalysed Arylation

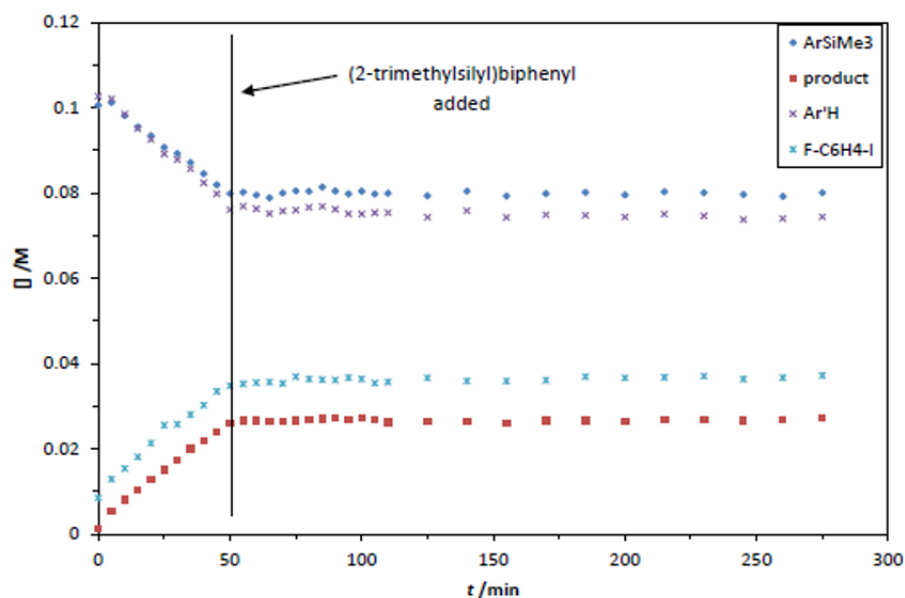
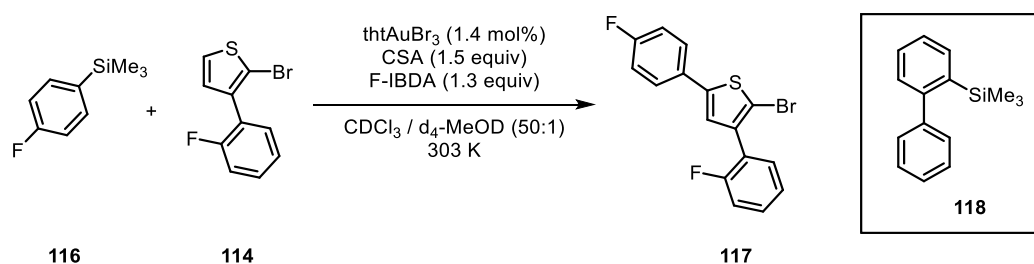
While *ortho*-substituted arylsilanes were found to be largely unreactive in arylation (or at least unable to form arylated products), a direct competition between *ortho*- and *para*-substituted silanes **112** and **113** was demonstrated to exhibit a surprising selectivity for the more sterically hindered arylsilane (Scheme 2.5).<sup>11</sup> This demonstrates that transmetalation is accelerated by substitution at the *ortho*-position rather than hindered by it, in agreement with the prior studies on electrophilic desilylations.<sup>7–9</sup> However, in contrast to Eaborn's findings on protodesilylation, in which the relative rate for **112** and **113** is similar, the gold-catalysed reaction appears to exhibit a significant steric acceleration effect for the *ortho*-methyl substituent. The reactivity of larger *ortho*-substituents in transmetalation to gold(III) was not

studied, with their reluctance to undergo arylation preventing straightforward analysis by the same method.



**Scheme 2.5.** Competition between *ortho*- and *para*-substituted arylsilanes.

In a prior mechanistic study on the arylation reaction, it was identified that addition of catalytic amounts of (*o*-biphenyl)trimethylsilane **118** to a gold-catalysed coupling reaction resulted in immediate stalling of catalysis, without any further consumption of silane, arene, or oxidant (Scheme 2.6).<sup>11</sup>

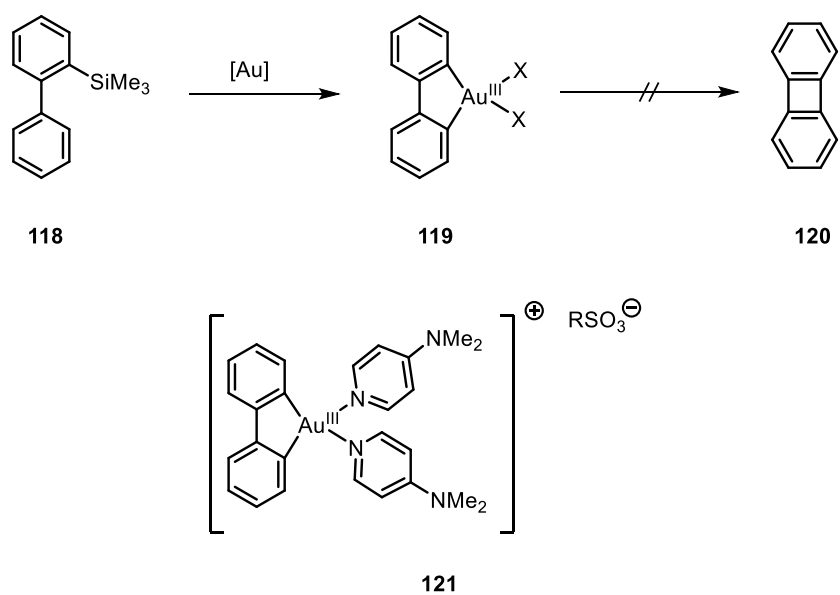


**Scheme 2.6.** Addition of (*o*-biphenyl)trimethylsilane to an intermolecular arylation reaction.<sup>ix</sup>

It was proposed that this was due to the formation of a highly stable cycloaurate species **119** which is unable to undergo reductive elimination to form the severely strained biphenylene product **120** (Scheme 2.7). Evidence in support of this was provided in the isolation of a DMAP coordinated, cycloaurated complex **121** from the resulting reaction mixture. Considering the established catalytic cycle, it was proposed that **118** acts as a potent catalyst poison by irreversibly competing for the gold(III) catalyst at the transmetalation step. The presence of an *ortho*-substituent in **118** offers a potential explanation for the observed potency of the catalyst poison, though the relative rate of transmetalation was not determined experimentally.

<sup>ix</sup> Figure reprinted with permission from *J. Am. Chem. Soc.* **2014**, 136, 254. Copyright 2018 American Chemical Society.



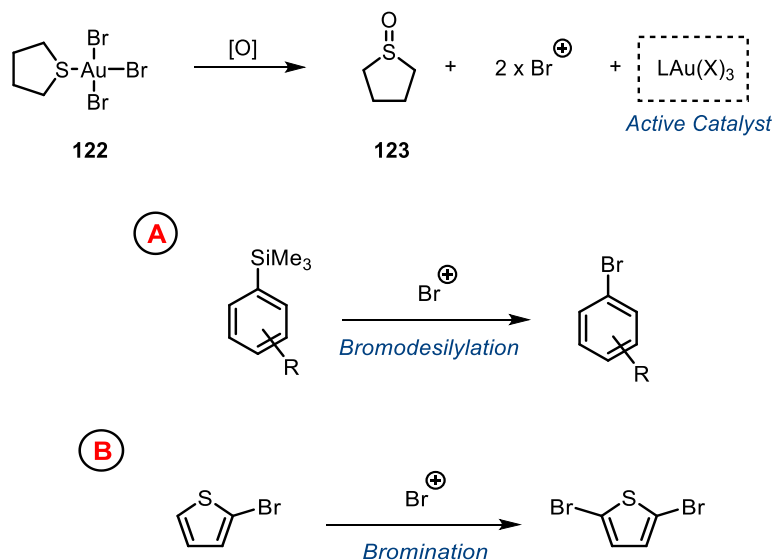


**Scheme 2.7.** Formation of a cycloaurated species following transmetalation (top) and the structure of isolated DMAP complex **121** (bottom).<sup>11</sup>

## 2.2 General Considerations

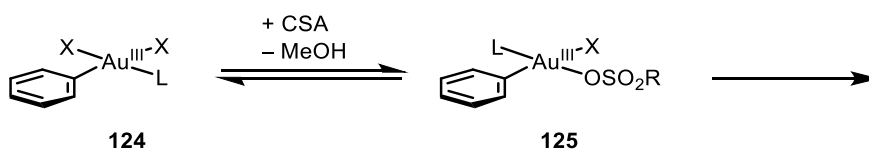
For the benefit of continuity, the reaction conditions for couplings reported in this chapter are based on those used in a prior mechanistic study.<sup>11</sup> The various components of the reaction serve a number of different roles that are essential for successful cross-coupling and/or straightforward reaction monitoring by *in situ* NMR spectroscopy.

thtAuBr<sub>3</sub> was demonstrated to be a convenient pre-catalyst for kinetic analysis due to its stability in chloroform solution (up to at least 1 month in dry CDCl<sub>3</sub> at 6–8 °C) and rapid activation to form the *in situ* active catalyst with absence of a significant induction period.<sup>11</sup> This activation proceeds with concurrent oxidation of the tetrahydrothiophene (tht) ligand to form sulfoxide **123** and an uncharacterised ring opened by-product, along with the loss of two of the three Br ligands (Scheme 2.8). Formally released as a source of “Br<sup>+</sup>”, associated bromination by-products (either bromodesilylation of the arylsilane, path **A**, or bromination of the arene, path **B**) can be observed in small quantities following activation of the pre-catalyst.



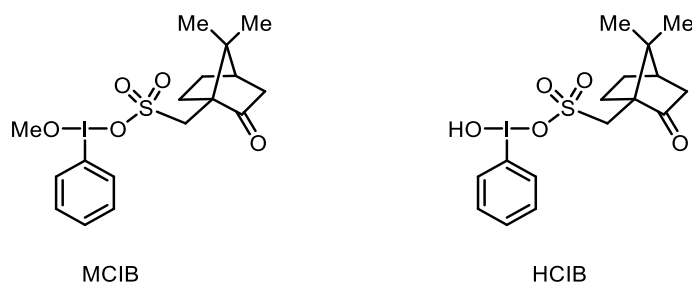
**Scheme 2.8.** Summary of the by-products generated during pre-catalyst activation.

Methanol is required to fully solubilise all of the reaction components, allowing for reproducible reaction kinetics to be observed by *in situ* NMR. However, there is also an inverse dependence on [MeOH] in the rate equation arising from inhibition of the turnover-limiting  $\pi$ -complexation event (Scheme 2.9).



**Scheme 2.9.** Requirement for exchange of MeOH with CSA prior to turnover-limiting arene  $\pi$ -complexation.

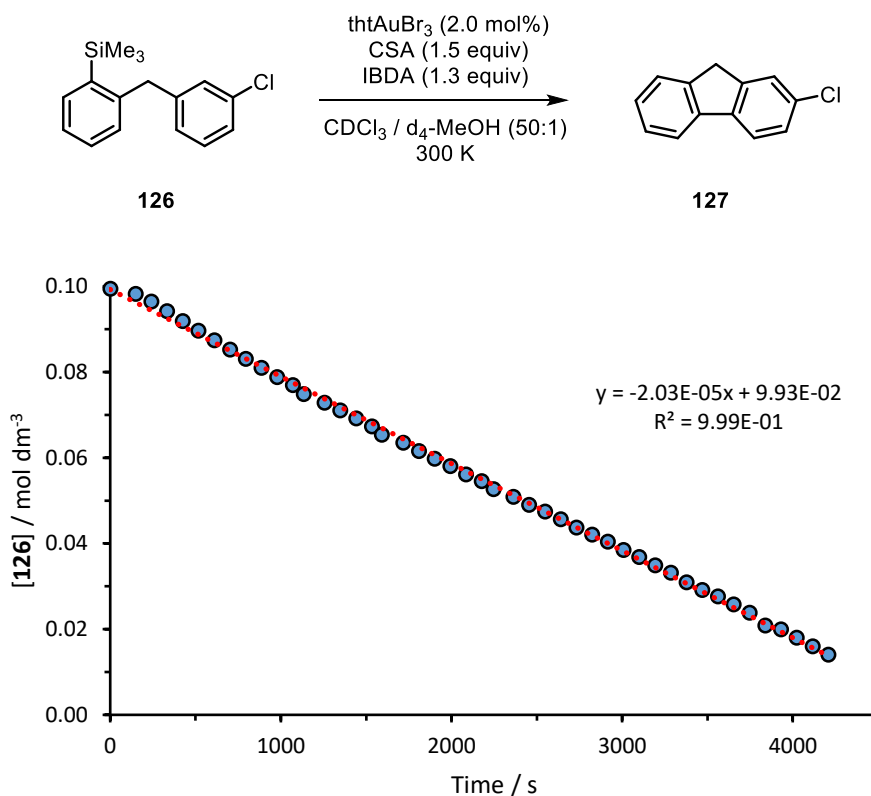
Iodobenzene diacetate (IBDA) is known to undergo rapid ligand exchange in the presence of sulfonic acids to form [hydroxy(sulfonyloxy)iodo]benzene species in both aqueous and organic reaction media.<sup>12–14</sup> It is therefore assumed that the active oxidant species under these reaction conditions is either MCIB (arising from reaction with methanol) or HCIB (arising from reaction with residual H<sub>2</sub>O) depending on how thoroughly dried the reaction solvent is prior to use (Figure 2.2). HCIB can be prepared and isolated independently,<sup>15</sup> and when used directly is equally as effective as the *in situ* generated oxidant.<sup>16</sup> Due to the necessity of ligand exchange between CSA and MeOH prior to  $\pi$ -complexation, there is a requirement that [CSA] > [IBDA] to ensure that there is always an amount of “free” CSA in solution.



**Figure 2.2.** Structures of the presumed active oxidant species in catalysis.

## 2.3 Initial Studies

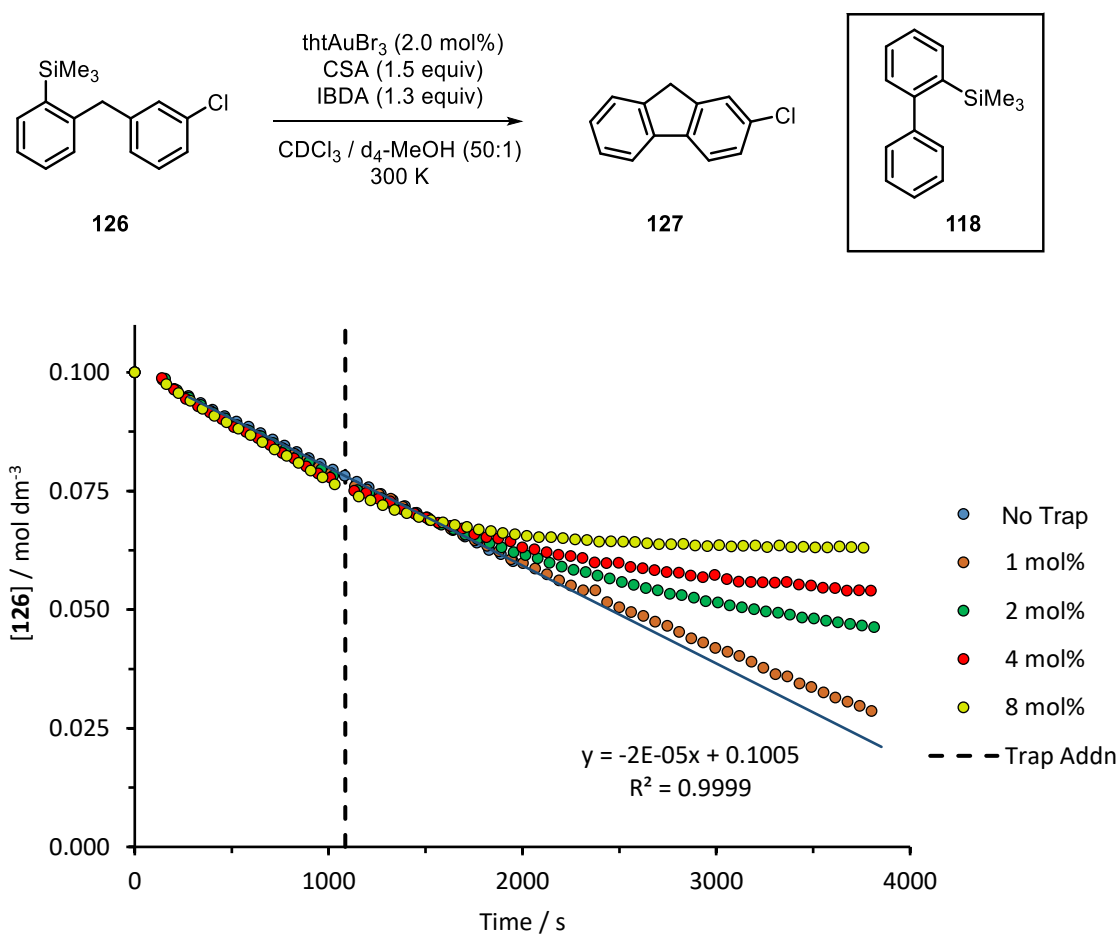
Substrates in which the arylsilane and arene coupling partners are tethered by a methylene unit (such as **126**) have been shown to cleanly undergo intramolecular coupling to form the corresponding fluorene products in almost quantitative yield (Scheme 2.10).<sup>17</sup> Unlike the analogous intermolecular arylation reactions, which exhibit a rate-dependence on the concentration of arene, these substrates display *pseudo-zero order* kinetics in which the rate of reaction is unaffected by changes in the concentration of substrate. As a result, concentration-time profiles for the reactions are greatly simplified.



**Scheme 2.10.** Concentration-time profile for the cyclisation of **126** to form **127**.

Taking the representative coupling of **126** to form fluorene **127**, it is possible to monitor the deviation in rate of reaction upon adding different quantities of the established catalyst poison **118** (Scheme 2.11). As the reaction profile in the absence of any additive is linear, with a gradient that corresponds the rate of reaction, it is visually much easier to assess the rate at which active catalyst is being sequestered. Addition of 1 mol% **118** is sufficient to cause notable deviation from the original rate of reaction (orange data points, Scheme 2.11). Increasing the amount of catalyst poison further leads to more pronounced curvature in the

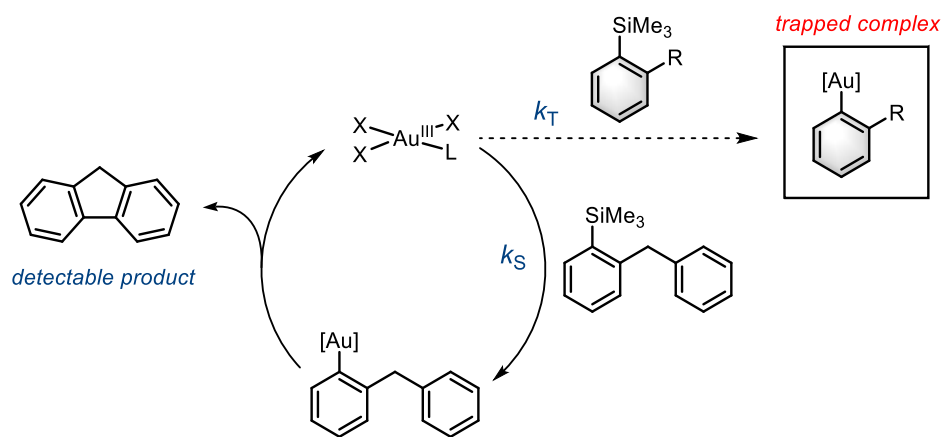
reaction profile, to the point that 8 mol% is sufficient to cause the reaction to promptly stall (blue data points, Scheme 2.11).



**Scheme 2.11.** Effect of additive **118** on the rate of product formation, across a range of concentrations.

This concentration dependence on the rate of trapping is indicative of a competitive removal of the catalyst whereby reaction with substrate **126** leads to productive turnover and product generation, while reaction with **118** irreversibly removes the catalyst from the reaction (Scheme 2.12).<sup>x</sup> As the first auration event is known to be silane transmetalation, the rate of catalyst trapping can be directly correlated to the relative partition at the transmetalation step between substrate and trap ( $k_S/k_T$ ).

<sup>x</sup> The term “trapping” is used throughout this chapter to describe the irreversible sequestering of active catalyst from the reaction by a catalyst “trap”, in this case *ortho*-substituted arylsilanes.

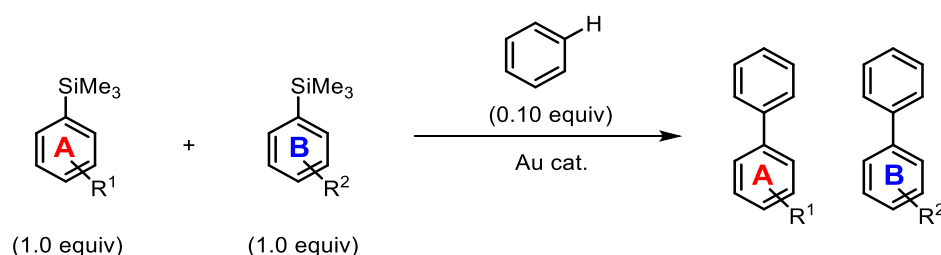


**Scheme 2.12.** Reaction stalling caused by competitive (irreversible) catalyst removal at the transmetalation step of the catalytic cycle.

## 2.4 Competition Experiments

### 2.4.1 Method of Analysis

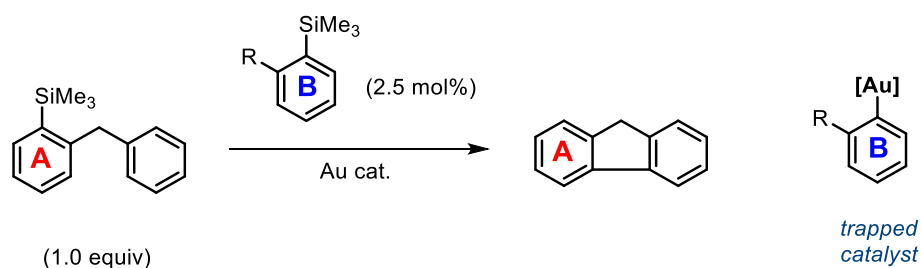
Conventional competition experiments, in which two substrates compete for a limiting amount of reactant or reagent, are typically analysed by the relative product distribution of the final reaction mixture (Scheme 2.13).<sup>18</sup> The ratio of the two (or more) products thus offers an approximation for the relative selectivity between the substrates, provided that a suitable excess is used to ensure that the concentration of available substrates does not change significantly as a function of conversion (typically >5 equivalents relative to the limiting reagent).



**Scheme 2.13.** General method for conventional competition experiments, analysed by product ratio.

However, if one of the substrates is unable to generate product and turnover the catalyst, then this method of analysis is not possible (as only one product will be formed). This is problematic in the case of *ortho*-substituted arylsilanes, which while able to transmetalate to the gold(III) catalyst, are unable to undergo cross-coupling to form a detectable product. One alternative is to perform the competition experiment with a stoichiometric amount of catalyst, but this is impractical if the catalyst cost is significant, or in this case, where complex catalyst activation processes render this type of analysis difficult.

Due to the simple reaction kinetics exhibited by the intramolecular variant of the arylation reaction, it is relatively straightforward to detect changes in catalyst concentration over the course of a reaction. This offers the possibility of a modified competition experiment whereby the partition between the two substrates is calculated based solely on the rate of formation of the competent coupling partner, product A (Scheme 2.14).



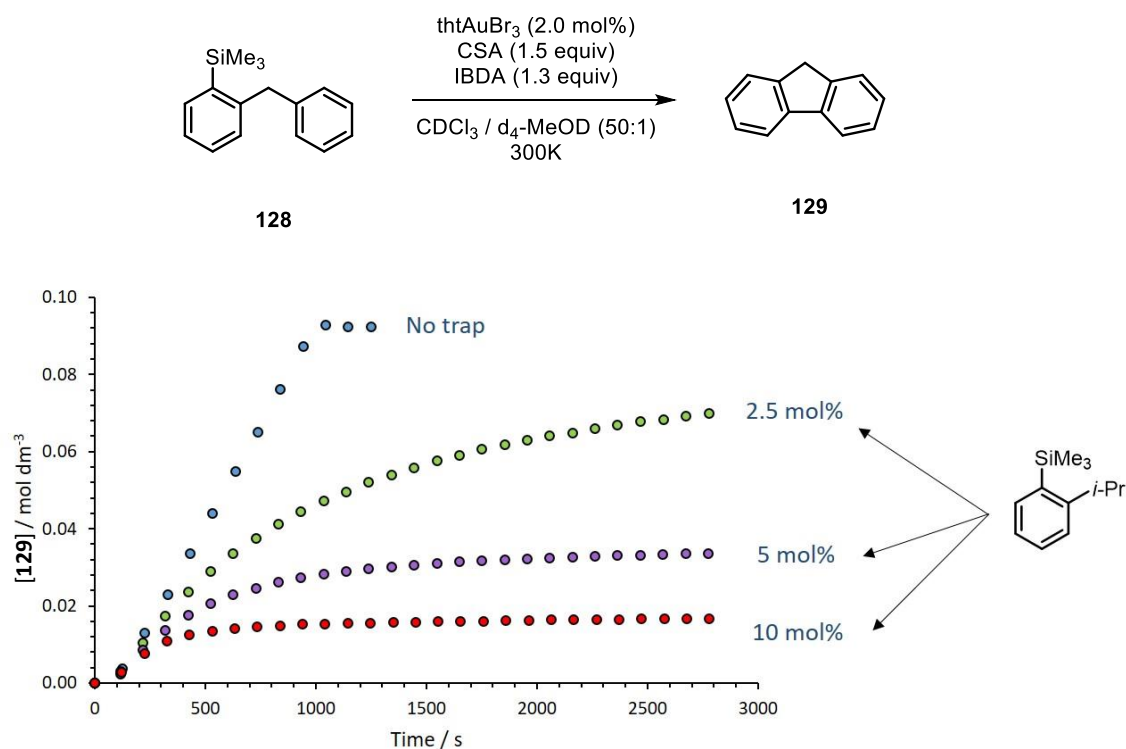
**Scheme 2.14.** Modified competition experiment, analysed by the change in rate of formation of product A.

Kinetic modelling of the reaction profile (across a range of different starting concentrations) allows the relative rate of transmetalation between substrate and trap to be calculated computationally. Comparison of these values across a series of structurally different arylsilane traps then provides a reactivity scale to be constructed for arylsilanes that cannot be analysed by conventional methods.

### 2.4.2 Reaction Monitoring

The intramolecular cyclisation of **128** to form **129** is a convenient benchmark reaction to use due to the ease of analysis by  $^1\text{H}$  NMR spectroscopy and short reaction time in the absence of any additives (Scheme 2.15). Based on the preliminary studies in Section 2.3, the amount of added arylsilane trap was varied over the range 0 – 10 mol% to ensure that a range of rates of reaction stalling were observed. For the benefit of consistency between experiments, and to ensure accurate concentrations could be determined, the ‘trap’ was present from the beginning of the reaction rather than added during the course of the reaction.





**Scheme 2.15.** The cyclisation reaction used in kinetic analysis (top) and an example of the typical appearance of concentration-time plots for trapping experiments (bottom).

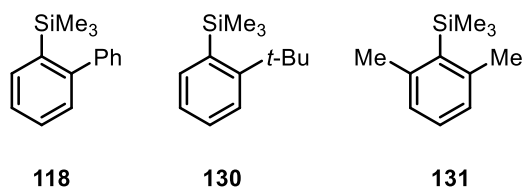
The above scheme provides a typical representation of the type of concentration-time graph generated for each individual *ortho*-substituted arylsilane. A minimum of four different sets of experimental data were obtained for each silane; one without any additive, and  $\geq 3$  with different additive concentrations. All graphs are shown as a function of product (**129**) formation but could equally display the decay of starting material (**128**), without any change to the method of analysis used (*vide infra*).

## 2.5 Kinetic Modelling

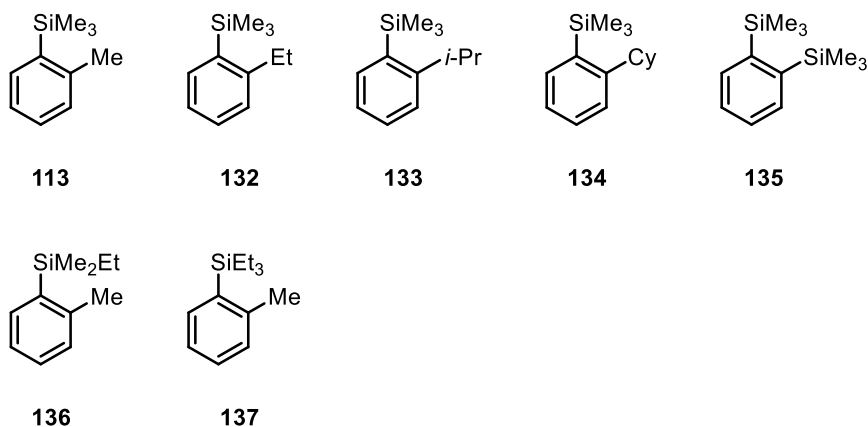
The construction of a robust kinetic model can allow rate constants and equilibria to be estimated computationally, based on experimental data. This can be particularly informative when it is not possible to directly measure the kinetics of certain steps in a catalytic cycle, or when the kinetic behaviour of a system is inherently complex. Using the concentration-time profiles described in Section 2.4, in conjunction with kinetic modelling software, it is possible to estimate the relative rate of transmetalation for the series of arylsilane ‘traps’. Experimental data was fitted using one of the two models discussed below (A or B) in order to calculate a ratio of transmetalation rates for each arylsilane trap;  $k_T/k_S$  (T = trap, S = substrate). Comparison of these values provides an indication of the structure-activity relationship across the series.

Representative examples of experimental data alongside the corresponding simulations are shown in the main body of the text. For a complete overview of reaction profiles and associated fitting see Appendix A.

### Model A:



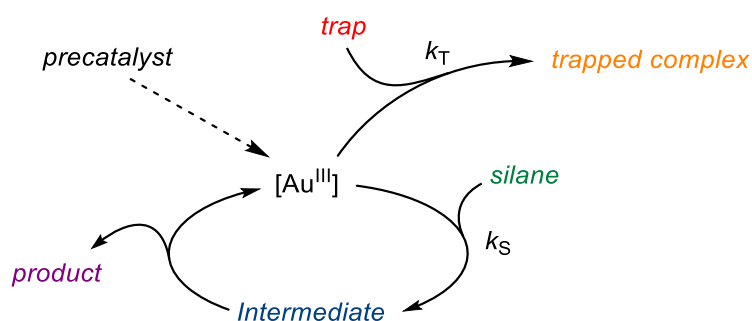
### Model B:



**Figure 2.3.** Overview of the series of *ortho*-substituted arylsilanes tested in trapping experiments.

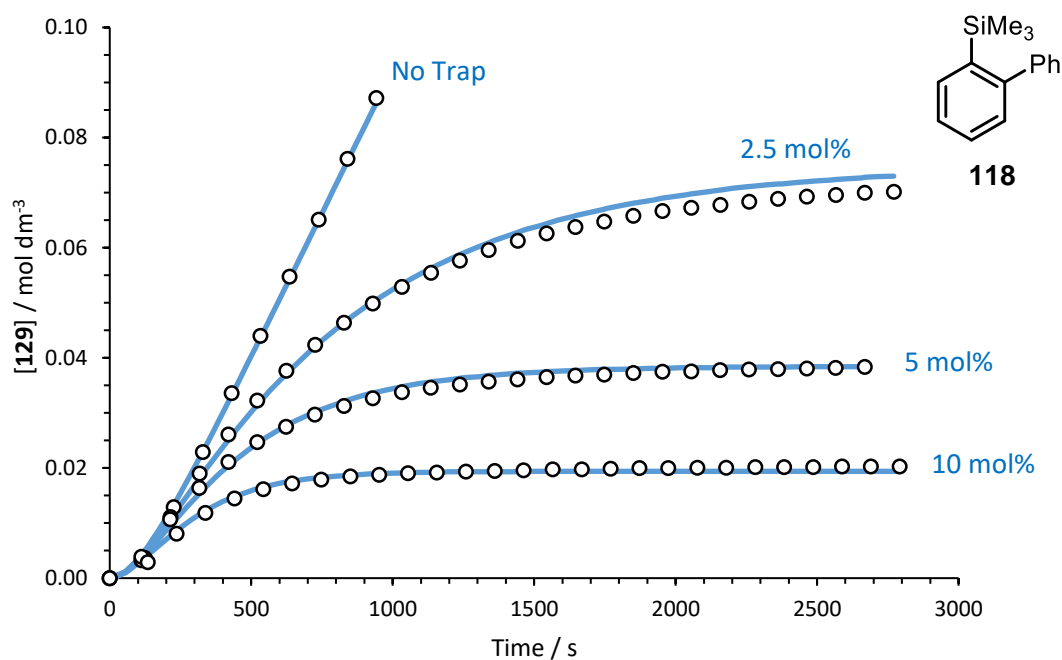
### 2.5.1 Model A

Arylsilanes **118**, **130**, and **131**, were fitted to the simple model (**Model A**) shown in Scheme 2.16. The model dictates that trapping is irreversible, such that only the ratio between  $k_T$  and  $k_S$  influences the curvature in the concentration-time plots.



**Scheme 2.16.** Visual schematic of Model A.

The pre-catalyst activation step also accounts for the generation of bromodesilylation products that are observed in small quantities (Scheme 2.8). As the substrate is present in vast excess over the trap, it is almost exclusively the component that is sacrificially consumed during pre-catalyst activation in most cases. However, bromodesilylation of the trap can become kinetically significant, especially for the more reactive *ortho*-substituted silanes. During the course of these investigations we noted that even slight errors in initial trap concentration can lead to poorly fitting simulations. In some cases, stoichiometric studies were carried out in order to calculate the amount of trap consumed during pre-catalyst activation (Appendix B).



**Figure 2.4.** Representative example of simulated model for trapping by **118**. White circles (experimental data points); blue lines (simulated reaction profiles).

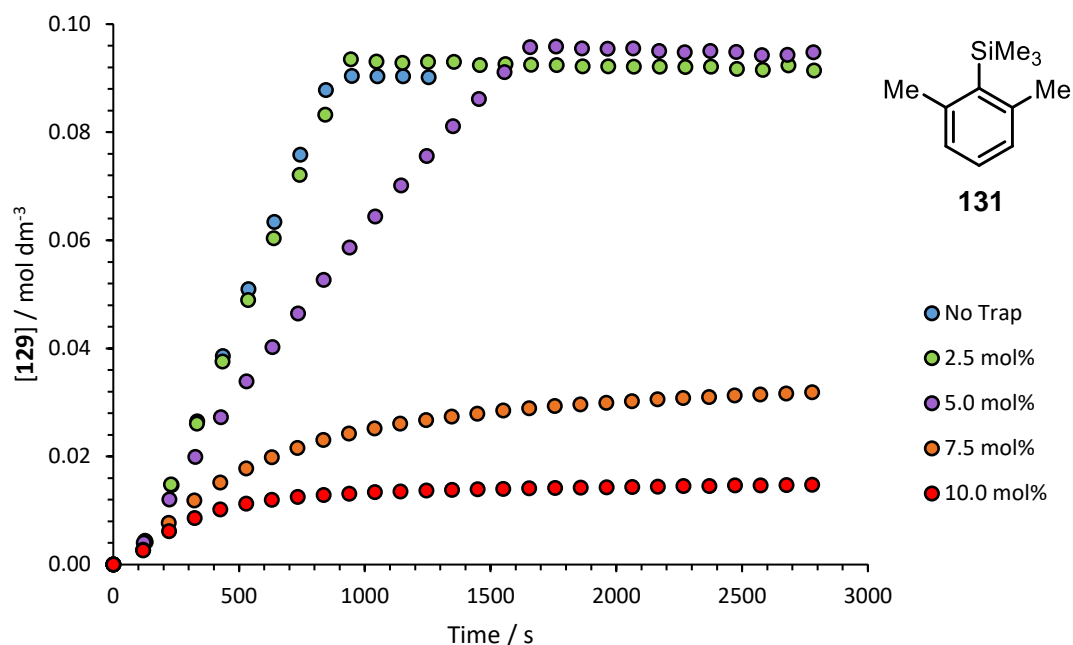
The results of the kinetic modelling for these arylsilane traps are summarised in Table 2.1. As expected, the more strongly electron donating *t*-Bu substituent was significantly more activating compared to the phenyl group in both bromodesilylation (during catalyst activation) and transmetalation to gold(III). It was calculated to be approximately six times more reactive than the cyclisation substrate in the initial bromodesilylation, corresponding to an effective loading of 2.1 mol% (rather than 2.5 mol%) for the smallest quantity added. In contrast, the independently measured value for the phenyl-substituted trap suggests that it is not reactive enough to significantly affect the initial trap concentration (exclusively the substrate is brominated).

**Table 2.1.** Relative rates for bromodesilylation (precatalyst activation) and transmetalation using Model A.

	<i>t</i> -Bu	Ph	2,6-Me
$k_{\text{Br-T}}/k_{\text{Br-S}}$	6.0 <sup>a</sup>	0.4 <sup>b</sup>	>50 <sup>a</sup>
$k_{\text{T}}/k_{\text{S}}$	<b>2.93</b>	<b>0.96</b>	<b>2.14</b>

[a] Calculated value; [b] Measured value.

(2,6-Dimethylphenyl)trimethylsilane **131** is an unusual case, due to its abnormally high reactivity in  $S_EAr$  chemistry compared to other *ortho*-substituted silanes (see Section 2.1.2). Such is the increase in reactivity, the trap is able to outcompete the substrate during pre-catalyst activation even though it is present in much lower concentration (Table 2.1). As a result, the concentration-time profile for the trapping experiments differ markedly in appearance compared to the rest of the series (Figure 2.5).

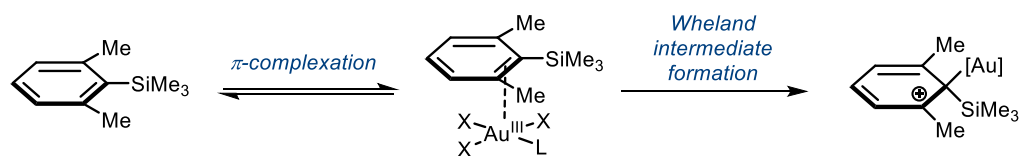


**Figure 2.5.** Concentration-time profile for trapping by **131**.

The reaction rate is entirely unaffected by addition of 2.5 mol% **131** as a result of the trap being fully consumed in pre-catalyst activation (a total of 4 mol% “Br<sup>+</sup>” must be sequestered). Increasing the trap loading to 5 mol% results in a straight-line plot with  $k_{\text{obs}} = 5.9 \times 10^{-5} \text{ s}^{-1}$ . This is consistent with rapid, but incomplete, trapping to remove a portion of the active catalyst (comparison of the gradients suggests an effective catalyst loading of approximately 1 mol%). As the initial trap concentration is increased further a more pronounced rate of stalling is observed, as sufficient trap survives pre-catalyst activation to fully sequester the catalyst.

The slower rate of transmetalation for the 2,6-disubstituted silane (compared to the *t*-Bu substrate) is best explained by an additional adverse steric effect. Considering the aforementioned steric relief argument, and the electron donating capability of the methyl substituents, **131** might be expected to transmetalate more readily. However, it is possible that

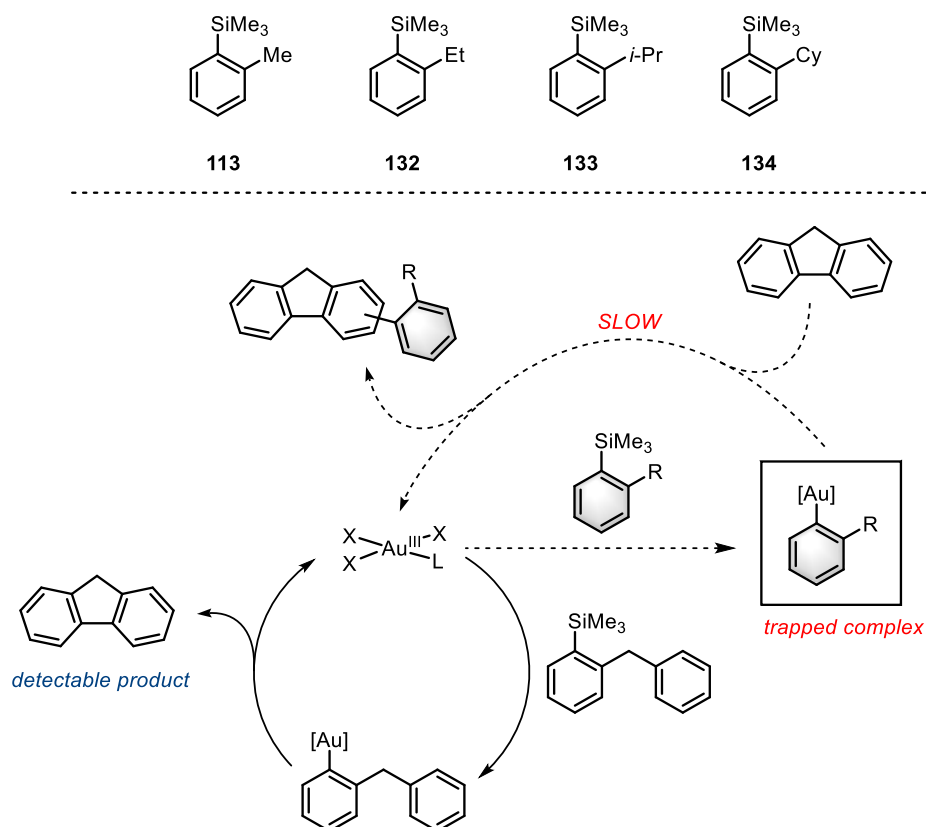
beyond a certain point, the approach of the incoming gold(III) electrophile (which is relatively large) is sufficiently hindered by the substitution that the preceding  $\pi$ -complexation becomes kinetically significant (Scheme 2.17).



**Scheme 2.17.** Necessary  $\pi$ -complexation prior to Wheland intermediate formation.

## 2.5.2 Model B

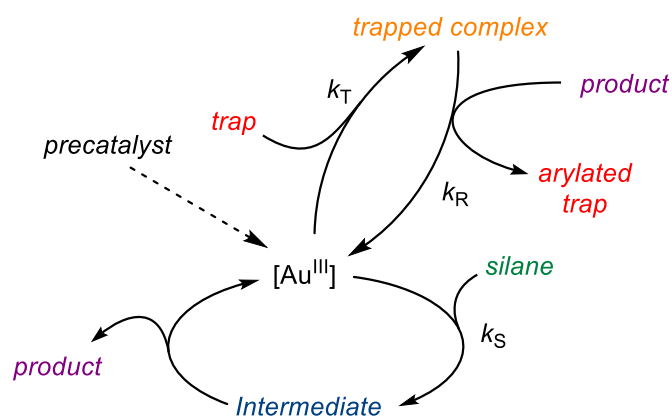
Arylsilanes **113**, **132**, **133**, and **134**, require a more complex description than the model in Scheme 2.16, as they are able to slowly react with the cyclised fluorene product to release the catalyst (Scheme 2.18).<sup>xi</sup> This renders the trapping somewhat reversible, though the rate of the intermolecular release reaction is calculated to be very slow in most cases.



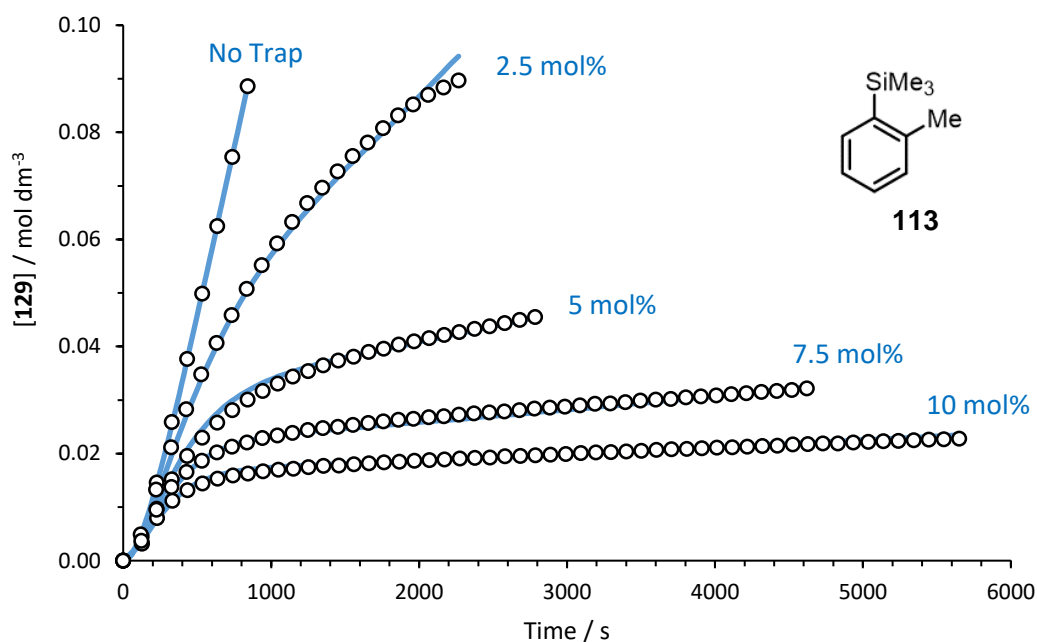
**Scheme 2.18.** Slow release of active catalyst by arylation of the trapped complex.

A slight modification to the model allows this to be accounted for and can actually provide calculated rate constants for the intermolecular coupling (**Model B**, Scheme 2.19). As might be expected, the rate of arylation decreases markedly from **113** to **132** and is much less significant for **133** and **134** (Table 2.2).

<sup>xi</sup> The arylated fluorene products have not been isolated and are only generated in trace amounts, but arylsilanes **113**, **132** and **133**, have been shown to undergo slow arylation with other arenes (see Section 3.1).



**Scheme 2.19.** Visual schematic of Model B.



**Figure 2.6.** Simulated fitting for trapping by **113** using model B.

The calculated rate constants for this class of *ortho*-substituted arylsilane are summarised in Table 2.2. The reactivity in transmetalation across the series covers a relatively narrow range, which is expected on electronic grounds, but implies that the effect of steric acceleration does not dramatically increase as the size of the neighbouring substituent is varied from methyl to cyclohexyl. However, the fact that the *t*-Bu substituent is approximately twice as activating can probably be attributed to a more pronounced steric alleviation affect, as the additional electron donating capability is not expected to be significant.<sup>19</sup>



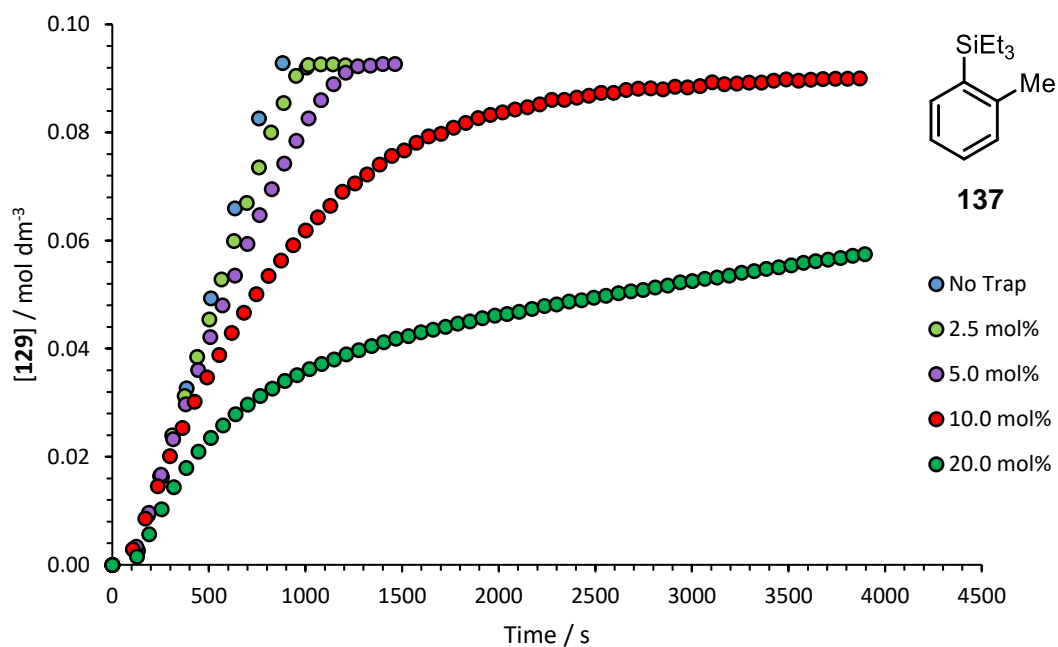
**Table 2.2.** Relative rates for bromodesilylation and transmetalation using Model B.

	Me	Et	<i>i</i> -Pr	Cy
$k_{\text{Br-T}}/k_{\text{Br-S}}$	3.3 <sup>a</sup>	3.6 <sup>a</sup>	3.2 <sup>a</sup>	3.1 <sup>a</sup>
$k_{\text{R}}$ (calculated) / dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup>	0.0040	0.0018	0.0008	0.0012
$k_{\text{T}}/k_{\text{S}}$	<b>1.23</b>	<b>1.54</b>	<b>1.34</b>	<b>1.31</b>

[a] Measured value.

### 2.5.3 Different Silyl Groups

Interestingly, arylsilanes **136**, and **137**, were also found to be capable of transmetalating to the gold catalyst. In the originally reported reaction screening, triethylarylsilanes were found to be unreactive, presumably unable to transmetalate under the reaction conditions.<sup>20</sup> However, *ortho*-methylation appears to sufficiently activate these less reactive silyl groups, that it enables them to transmetalate at room temperature.

**Figure 2.7.** Concentration-time profile for trapping by arylsilane **137**.

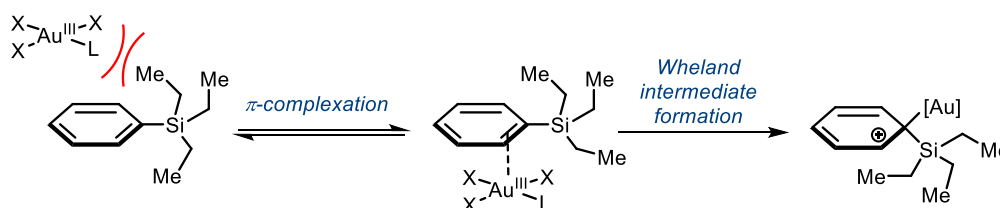
Triethylsilane **137** is significantly less reactive than the analogous trimethylsilane **113**, and as a result has a notably different concentration-time profile for trapping (Figure 2.7). Much higher trap loadings are required to cause the reaction to stall, with  $\leq 5$  mol% resulting in only minor deviation from the uninhibited reaction. The calculated rates of transmetalation suggest that the trimethyl-substituent is approximately six times more reactive, with the dimethylethylsilyl-group falling somewhere in between (Table 2.3).

**Table 2.3.** Relative rates for bromodesilylation and transmetalation of different silyl groups using Model B.

	-SiMe <sub>3</sub>	-SiEtMe <sub>2</sub>	-SiEt <sub>3</sub>
$k_{\text{Br-T}}/k_{\text{Br-S}}$ (measured)	3.3 <sup>a</sup>	< 0.5 <sup>b</sup>	< 0.5 <sup>b</sup>
$k_{\text{T}}/k_{\text{S}}$	<b>1.23</b>	<b>0.73</b>	<b>0.19</b>

[a] Measured value; [b] Calculated value.

This order of reactivity is opposite to that expected based on the inductive electron releasing effects of the substituents at silicon (inductive effects should better stabilise the Wheland intermediate). Similar to the 2,6-disubstituted system, it is likely that the larger substituents on silicon hinder  $\pi$ -complexation of the gold(III) species to the aryl group, resulting in slower rates of transmetalation (Scheme 2.20).<sup>xii</sup> This trend in reactivity is in agreement with studies on protodesilylation in which silyl groups were found to decrease in reactivity in the following order: SiMe<sub>3</sub> > SiEt<sub>3</sub> > Si(*n*-Pr)<sub>3</sub> > Si(*i*-Pr)<sub>3</sub>.<sup>21,22</sup>

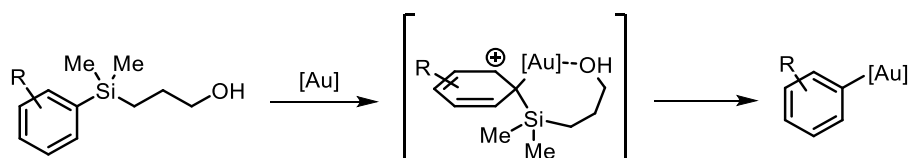


**Scheme 2.20.** Possible blocking effect by the ethyl groups of the triethylsilyl substituent.

<sup>xii</sup> The larger silyl groups could also be expected to influence solvation of the Wheland intermediate, as postulated by Eaborn.<sup>31</sup>

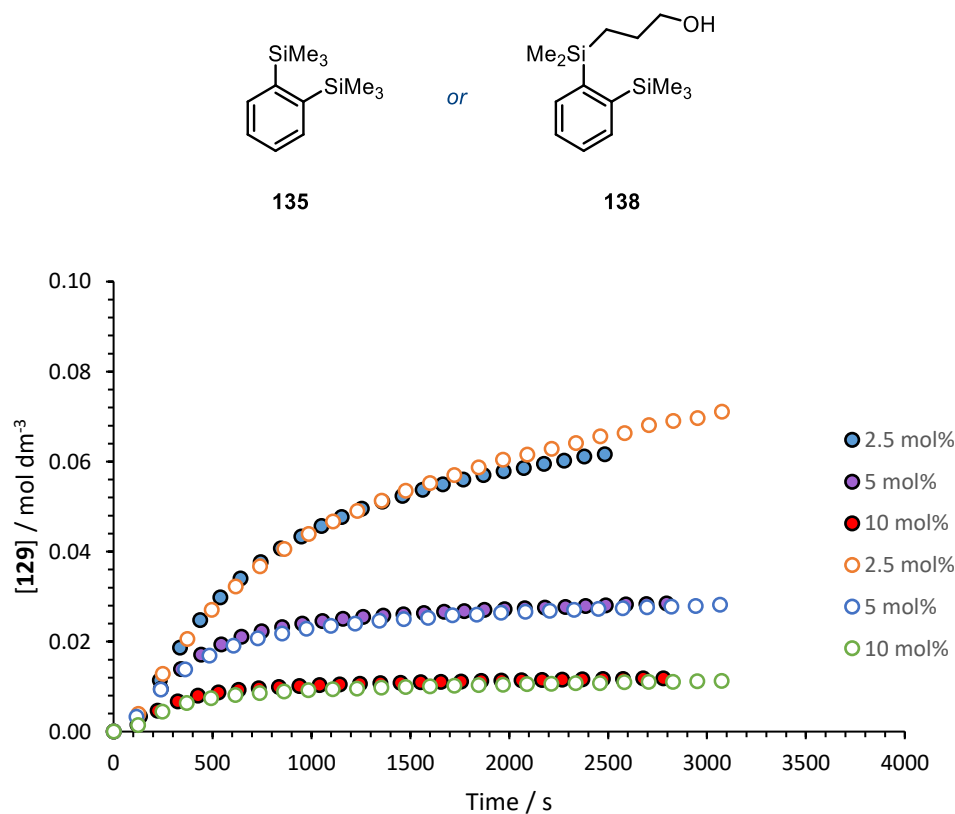
### 2.5.4 HPDMS Examples

In intermolecular cross-coupling, the hydroxypropyldimethylsilyl group (HPDMS) was found to significantly accelerate the rate of transmetalation – estimated to be approximately 5 times faster than the trimethylsilyl analogue.<sup>2,23</sup> This effect is attributed to pre-complexation of the catalyst, followed by an intramolecular delivery of the gold catalyst from the pendant alcohol of the silyl group (Scheme 2.21).

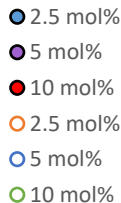


**Scheme 2.21.** Intramolecular delivery of catalyst by HPDMS group.

While the effect was assumed to be general across a range of substituted HPDMS reagents, *ortho*-substituted arylsilanes **138** and **139**, exhibited a similar rate of transmetalation (within error) to the analogous trimethylsilyl- analogues when subjected to the same trapping experiment conditions (Figure 2.8 and 2.9).



**Figure 2.8.** Comparison of trapping by trimethylsilane **135** and HPDMS silane **138**. Filled circles (**135**); hollow circles (**138**).



circles (133); hollow circles (139).

This demands that the effects governing rate acceleration in both cases (*ortho*-substitution and modified silyl reagents) are not additive in nature. It is possible that the presence of a large *ortho*-substituent hinders (or altogether prevents) the intramolecular delivery (Scheme 2.22). Alternatively, the *ortho*-effect may simply be dominant such that the pre-complexation no longer provides a noticeable rate enhancement.



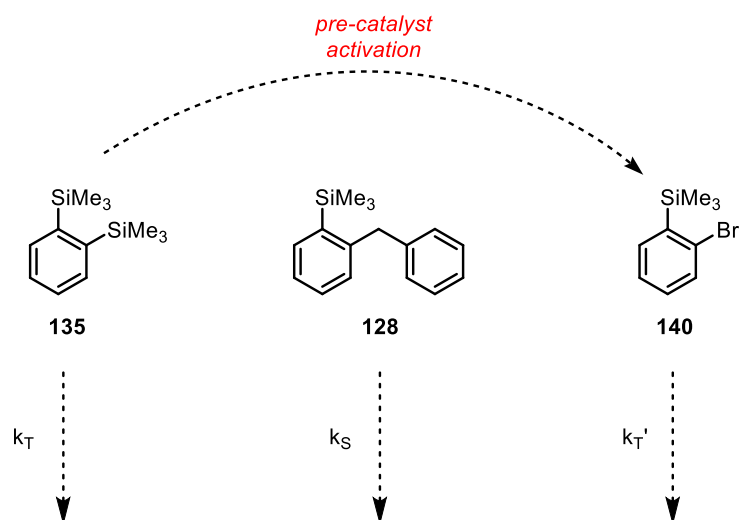
**Scheme 2.22.** Hindered intramolecular delivery due to ortho-substitution of the arylsilane.

### 2.5.5 Limitations

The kinetic profile of the reaction is highly sensitive to small changes in catalyst and trap concentration, and thus necessitates very careful preparation of samples using stock solutions (see Appendix C for a full discussion). Even with such precautions, a degree of error in the final calculated values can be expected, arising from slight inaccuracies in the starting concentrations used. The use of at least four individual sets of experimental data in the construction of each model helps to mitigate this, although a number of repeat experiments would offer a greater degree of certainty in the final values.

The use of  $\text{tHtAuBr}_3$ , although convenient in its absence of induction period, poses a number of complications to analysis. Two bromide ligands must be lost during catalyst activation (formally as  $\text{Br}^+$ ), and in turn consume a small amount of arylsilane through bromodesilylation. This has an impact on the initial concentrations of substrate and 'trap', both of which may be brominated, and must be accounted for in the kinetic model.

Analysis of trapping by 1,2-bis(trimethylsilyl)benzene (**135**) proved particularly problematic, with attempts to simulate experimental data using either model resulting in unsatisfactory fits. This indicates that the kinetic model does not provide a good description of the chemical system in this instance. Significant steric acceleration effects have been observed in protodesilylation studies for neighbouring trimethylsilyl- substituents,<sup>8</sup> and therefore the amount of trap consumed during pre-catalyst activation is likely to be significant (similar to the 2,6-dimethyl-substituted case). The product of bromodesilylation (**140**), can likely also undergo transmetalation, leading to a complex three-way competition for the active catalyst (Scheme 2.23). Deconvolution of the system is non-trivial and an accurate determination of relative transmetalation rates would require an alternative method.



**Scheme 2.23.** Complex three component competition in the case of arylsilane trap **135**.

## 2.6 Summary

Using a combination of *in situ* reaction monitoring and kinetic modelling, the rate of transmetalation for a series of *ortho*-substituted arylsilanes has been calculated. This method of analysis allows relative rate constants to be calculated even though the substrates of interest are unable to generate arylated products, and therefore offers an alternative protocol to conventional competition experiments.

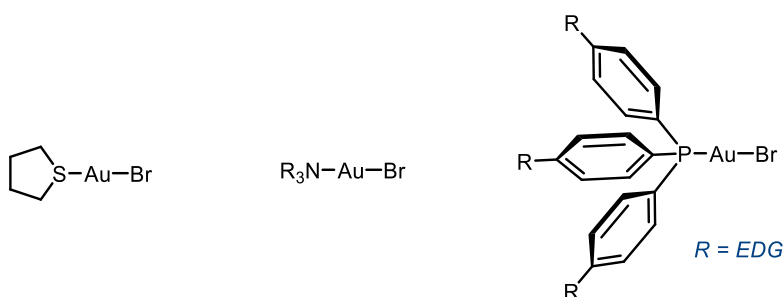
In contrast to the previously held perception that *ortho*-substituted arylsilanes are unreactive in gold catalysis, the transmetalation of arylsilanes to gold(III) has been found to be significantly accelerated by substitution at the *ortho*-position, an affect attributed to the alleviation of steric strain upon formation of the Wheland Intermediate. While it is difficult to fully separate steric and electronic contributions to the rate of transmetalation, it appears that a significant, and favourable, steric relief effect is observed for the entire series of *ortho*-substituents examined in this study.

It had previously been thought that the gold-catalysed arylation and related reactions were limited to the use of aryltrimethylsilane reagents.<sup>24–27</sup> However, it is now apparent that the presence of an *ortho*-substituent is able to ‘activate’ larger silyl groups to transmetalate to gold under ambient conditions. The *o*-tolyl derived arylsilanes were found to react less rapidly as the size of the alkyl groups at silicon was increased, possibly by obstructing the approach of the incoming gold complex.

## 2.7 Future Work

### 2.7.1 Method Improvements

The results discussed in this chapter offer a comprehensive but largely qualitative analysis of the transmetalation of *ortho*-substituted arylsilanes to gold(III). While the described method of kinetic analysis allows the accurate calculation of rate constants by competition, the complex nature of the gold-catalysed arylation reaction introduces a degree of uncertainty to the calculated rate constants. In light of this, the system could be vastly simplified by the identification of a pre-catalyst that does not consume any arylsilane reagent(s) during activation. As the reaction is known to be sensitive to the nature of the remaining anionic ligand following activation,<sup>11</sup> future endeavours should perhaps focus on readily activated gold(I) bromide derived pre-catalysts (Figure 2.10).



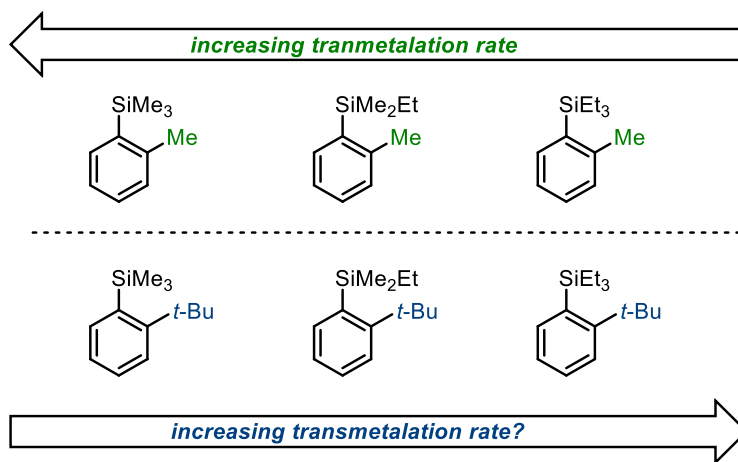
**Figure 2.10.** Potential gold(I) bromide pre-catalysts that could be easily activated by protonation or oxidation.

In order to fully understand the limitations of the trapping-kinetic modelling approach to competition experiments, a comparison against an established, well-studied process would be valuable. This would provide an indication as to how the degree of error in the calculated values varies as a function of the number of experiments carried out (how many different concentrations are needed). Generating large volumes of kinetic data is time consuming (particularly with respect to analytical instrument use), and therefore performing the minimum number of experiments required to generate reliable data is an important consideration.

### 2.7.2 Alternative Silyl Groups

Silyl groups that were previously thought to be unable to transmetalate to gold(III) were found to be 'activated' by *ortho*-methylation. Though the rate of transmetalation was found to

decrease across the series in Figure 2.11, it remains unclear if this trend remains consistent for larger *ortho*-substituents. While approach of the gold(III) species may be hindered to some extent, the unfavourable steric interactions in the ground state could be expected to increase markedly. As a result, the order of reactivity may be significantly altered, perhaps even to the point that bulkier silyl groups react fastest.



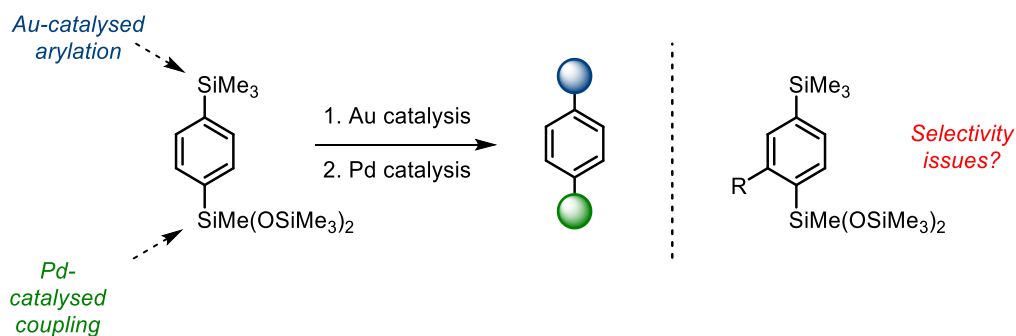
**Figure 2.11.** Potential reversal of reactivity for larger *ortho*-substituents.

The demonstration that other silyl groups may be compatible coupling partners in gold catalysis is interesting for a number of reasons. Firstly, the synthesis of aryltrimethylsilanes typically necessitates the preparation of an organometallic reagent (usually an aryl lithium or Grignard), and subsequent reaction with trimethylsilyl chloride.<sup>28,29</sup> While this is a reliable and high yielding method, it restricts the number of functional groups that can be readily incorporated into the arylsilane.<sup>xiii</sup> There are comparably more synthetic methods that are able to introduce larger silyl groups, owing to the ease with which the corresponding silyl hydrides can be handled ( $\text{HSiMe}_3$  is a gas at room temperature), and which are often tolerable of a range of functional groups.<sup>30</sup>

Secondly, the assumption that larger arylsilane groups are benign under the reaction conditions required for gold catalysis must be reconsidered if there is neighbouring substitution. Substrates that may have been considered as candidates for sequential couplings may suffer from a lack of regiocontrol as a result of unwanted C-Si auration (Scheme 2.24).

<sup>xiii</sup> Some palladium-<sup>32,33</sup> and rhodium-<sup>34,35</sup> catalysed methods for the synthesis of aryltrimethylsilanes using HMDS have also been reported, though arylhalide substituents are poorly tolerated.

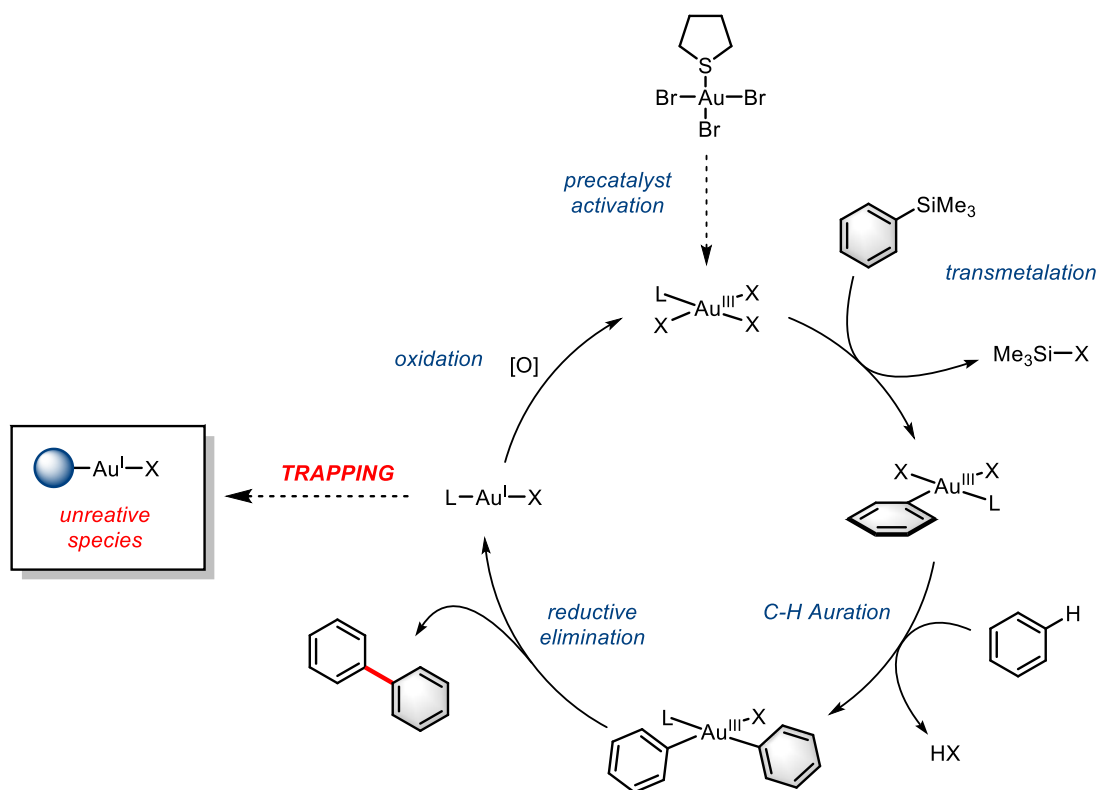




**Scheme 2.24.** Potential selectivity issues caused by *ortho*-substitution of other silyl groups.

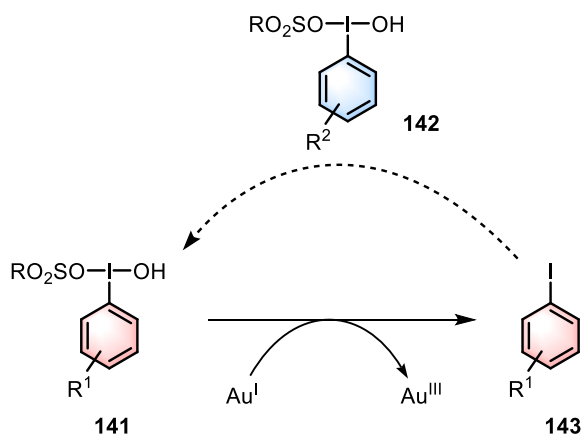
### 2.7.3 Further Applications of Trapping-Kinetic Modelling Approach

The design of suitable catalyst traps could allow interrogation of other steps in the catalytic cycle. For example, a reagent that selectively reacts with gold in oxidation state +1 could be used to probe the mechanism of Au(I)/Au(III) oxidation (Scheme 2.25); a process that is poorly understood in many gold-catalysed reactions.



**Scheme 2.25.** Proposed trapping experiment to investigate the oxidation step of the catalytic cycle.

Conventional competition reactions between two electronically differentiated iodine(III) reagents are complicated by the possibility of equilibration between the oxidant species. This issue could be bypassed by a trapping-modelling method, provided that the trap was designed to only interact with the gold(I) intermediate.



**Scheme 2.26.** Possible equilibration between iodine(III) reagents that complicates competition experiments.

The modified competition experiment used in this work has thus far been exclusively applied to oxidative gold-catalysed direct arylation. However, other transition metal-catalysed processes could feasibly be treated by an analogous method. The use of a system that exhibited zero-order kinetics greatly simplified the analysis in this case, but in principle the reaction order is not important provided that it is incorporated into the kinetic model. The trap component must be designed such that it can only interact with the catalyst at one step of the catalytic cycle, a characteristic that may be problematic in some metal-catalysed reactions.

## 2.8 References

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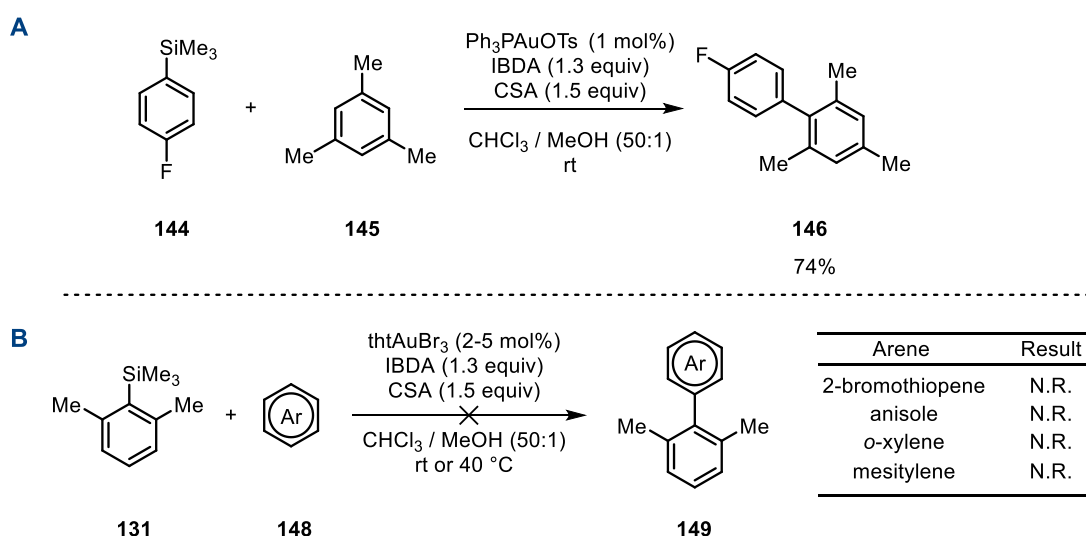
### **Design of *ortho*-Substituted Arylsilanes for Coupling**

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### 3.1. Introduction

The results discussed in Chapter 2 demonstrate that even severely hindered arylsilane reagents can effectively transmetalate to the gold(III) catalyst species used in direct arylation. Interestingly, this suggests that intermolecular arylation of these reagents is inhibited at a different step of the catalytic cycle, for example  $\pi$ -complexation, C–H auration, or reductive elimination.

The coupling of arylsilane **144** and mesitylene **145** occurs under standard reaction conditions, at room temperature, to afford the coupled product **146** in good yield (**A**, Scheme 3.1).<sup>1</sup> In contrast, 2,6-disubstituted arylsilane **131** does not undergo any reaction with a variety of arenes, even at elevated temperatures or with increased catalyst loadings (**B**, Scheme 3.1).



**Scheme 3.1.** Attempted arylation of **131** under typical reaction conditions.

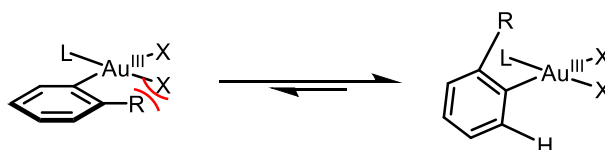
Both sets of reactions could be expected to proceed through similar arylgold(III) intermediates prior to reductive elimination (Figure 3.1), precluding this step as a reasonable explanation for the observed lack of reactivity.



**Figure 3.1.** Hypothetical pre-reductive elimination structures for both coupling reactions (S = Silane; A = Arene).

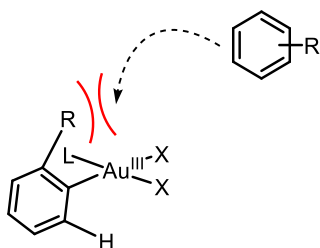
A conformational equilibrium that favours a perpendicular geometry of the aryl group can be expected on steric grounds for *ortho*-substituted ring systems, as has been inferred in

analogous square planar complexes of the  $M^{2+}$  group 10 metals (Scheme 3.2).<sup>2</sup> The more sterically imposing the substituent, the further this equilibrium can be anticipated to be biased toward the perpendicular geometry (right), avoiding increasingly unfavourable steric clashes with the neighbouring ligands.



**Scheme 3.2.** Conformational equilibrium for arylgold(III) species.

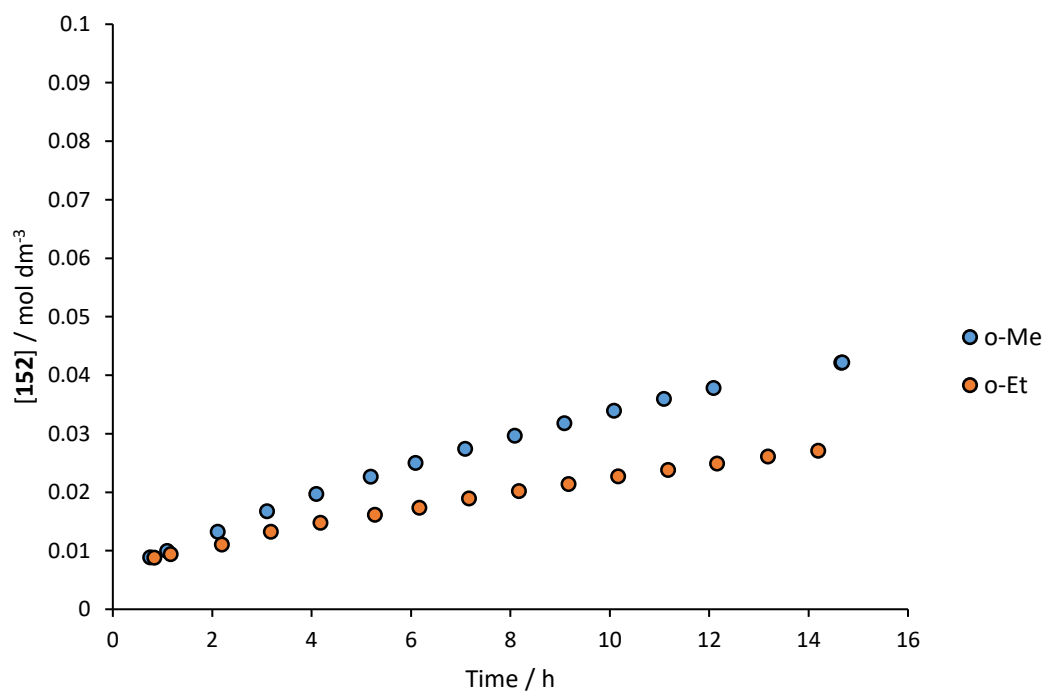
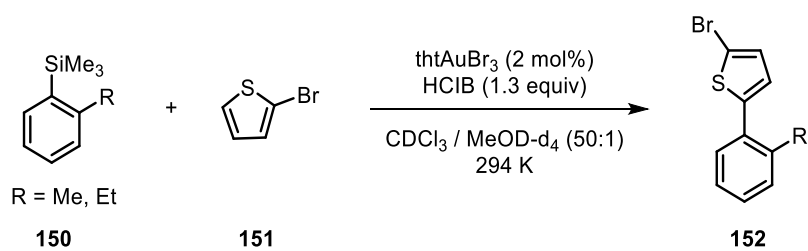
Based on present understanding of the reaction mechanism, the turnover-limiting  $\pi$ -complexation of the arene coupling partner is proposed to occur *via* an associative pathway.<sup>3</sup> Evidence in support of this includes a significant negative entropy of activation ( $\Delta S^\ddagger = -26.5 \pm 0.5 \text{ cal K}^{-1} \text{ mol}^{-1}$ ), first order dependence on the arene coupling partner, and the fact that the arylation step occurs at an electrophilic gold(III) centre (in contrast to gold(I)). Based on this information, and the conformational equilibrium described in Scheme 3.2, it is likely that *ortho*-substitution of the arylsilane would hinder  $\pi$ -complexation by blocking the approach of the incoming arene above and below the square planar species (Figure 3.2).



**Figure 3.2.** Proposed blocking effect resulting from *ortho*-substitution of the arylsilane.

The trend in reactivity for simple *ortho*-alkyl substituted arylsilanes is in agreement with this hypothesis, with decreasing rates of reaction observed across the series  $\text{Me} > \text{Et} > i\text{-Pr}$  (Scheme 3.3), and larger substituents completely preventing the coupling reaction (no reaction observed in the case of *t*-Bu). As the size of the neighbouring group increases, the population of catalyst in the conformation required for reaction is necessarily reduced according to the equilibrium in Scheme 3.2, and a reduction in the rate of reaction is observed.



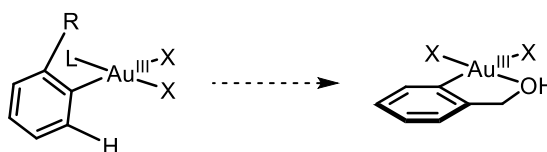


**Scheme 3.3.** Rates of coupling with 2-bromothiophene (**151**) for *ortho*-substituted arylsilanes.

## 3.2. Tethered Ligands

### 3.2.1. Initial Results

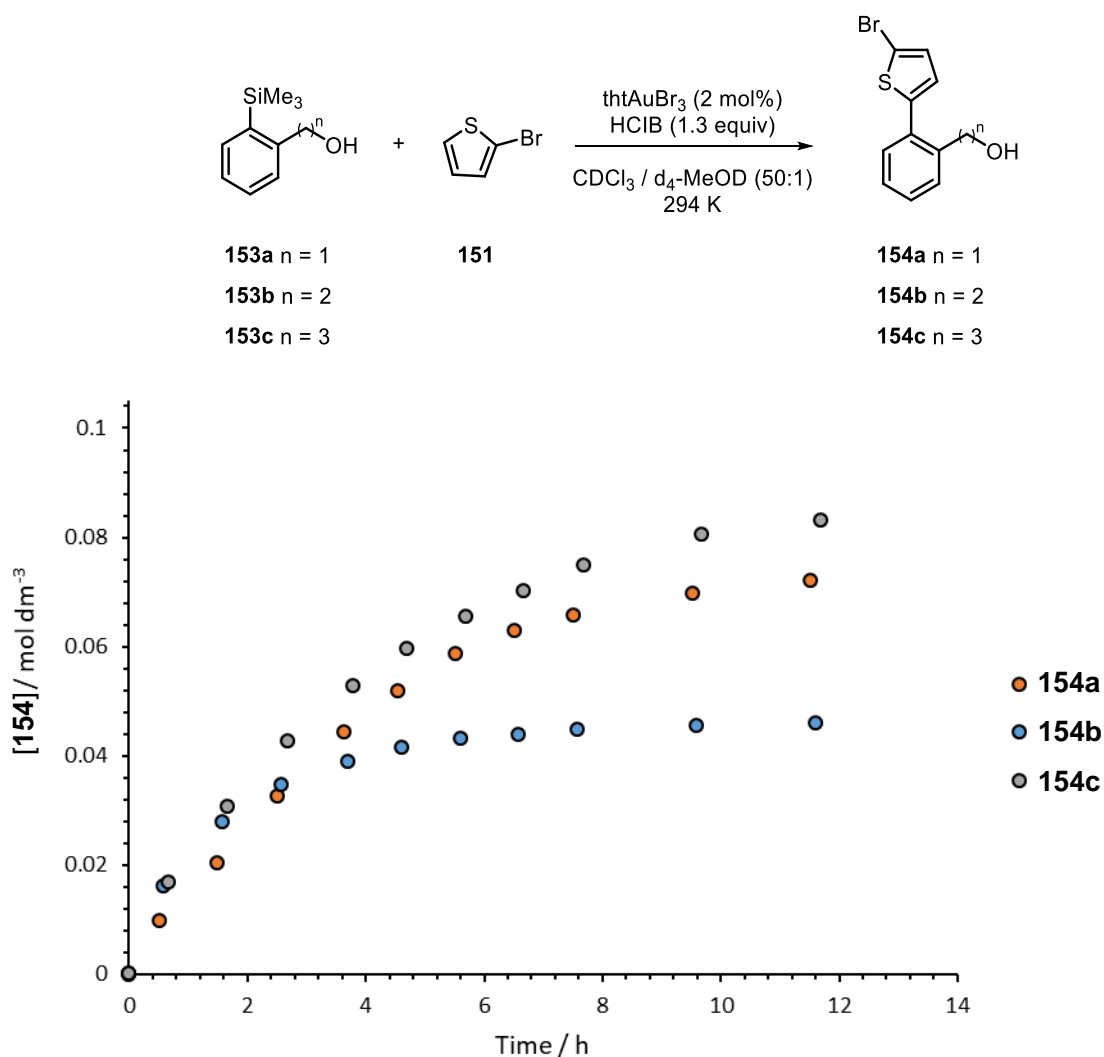
Considering the perpendicular geometry hypothesis described in Scheme 3.2, it follows that if the equilibrium could be artificially biased toward the reactive conformation, then the  $\pi$ -complexation event and subsequent bond formation should be more favourable. To this end, we hypothesised that the introduction of a Lewis basic moiety tethered to the arylsilane might be able to act as a chelating ligand and force the aryl group to adopt the planar geometry required for catalysis (Scheme 3.4).



**Scheme 3.4.** Anticipated conformational control through chelation.

Gold(III) complexes are generally considered to be highly oxophilic,<sup>4,5</sup> and the methanol co-solvent of the reaction is known to act as a labile ligand at certain points in the catalytic cycle.<sup>3,6</sup> Likewise, modification of the silyl group to incorporate a pendant alcohol was found to significantly affect the rate of transmetalation,<sup>7</sup> presumably through pre-complexation of the catalyst (see Section 2.5.4). Therefore, anticipating that an oxygen-containing substituent might coordinate with sufficient strength to alter the conformation of the aromatic ring, arylsilanes **153a**, **153b**, and **153c**, bearing a pendant alcohol, were synthesised to test this hypothesis (Scheme 3.5).<sup>xiv</sup>

<sup>xiv</sup> In Toste's gold-catalysed oxyarylation using aryltrimethylsilanes, the only *ortho*-substituted silane demonstrated to undergo coupling was a primary alcohol.<sup>66</sup>

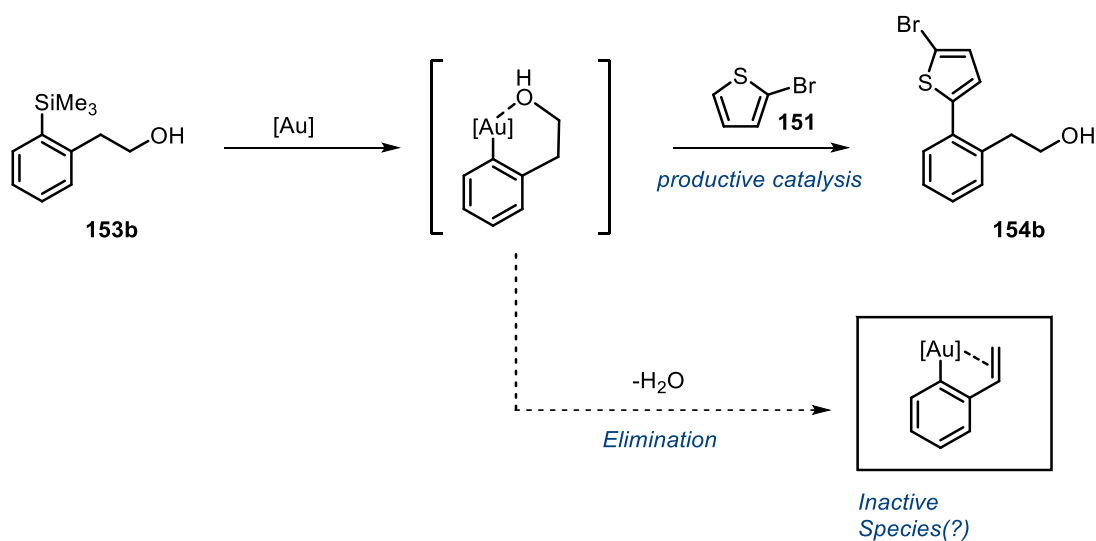


**Scheme 3.5.** Reactivity of alcohol-containing silanes **153a**, **153b**, and **153c** in arylation with 2-bromothiophene. [silane] = [arene] = 0.1 M.

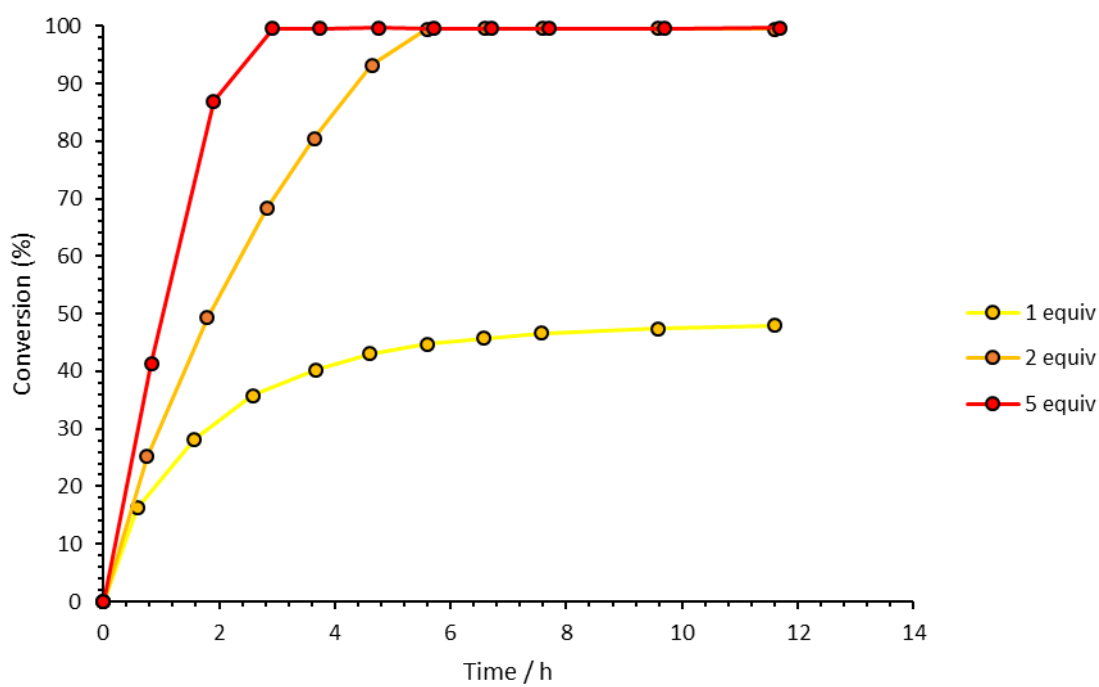
In stark contrast to most *ortho*-alkyl substituted silanes, these reactants readily underwent intermolecular coupling with 2-bromothiophene<sup>xv</sup> at ambient temperature (Scheme 3.5). The length of the tether could be extended to at least three methylene units without a significant change in reactivity (extended tethers were not tested), although the reaction with **153b** stalled at approximately 50% conversion. In the case of this substrate, it is possible that a competitive elimination to form a styrene might occur, resulting in an inactive off-cycle species (Scheme 3.6). Arylsilanes possessing tethers of different lengths (such as **153a** and **153c**) are

<sup>xv</sup> 2-Bromothiophene is a convenient arene to use in the arylation reaction due to its moderate reactivity and near complete regioselectivity for the 5-position.

unable to undergo an analogous elimination (formation of a conjugated alkene is not possible), offering an explanation as to why the reaction does not stall in those instances.



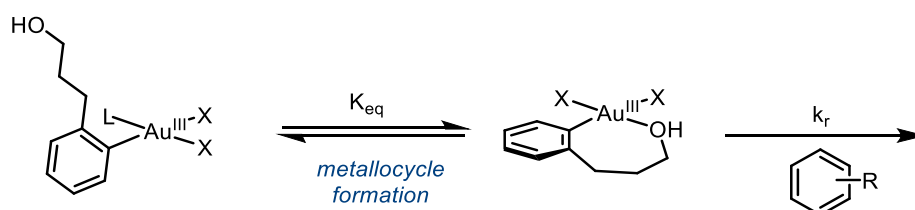
**Scheme 3.6.** Plausible explanation for the observed stalling in the reaction with **153b**.



**Figure 3.3.** Effect of varying equivalents of arene coupling partner (**151**) on reaction stalling.

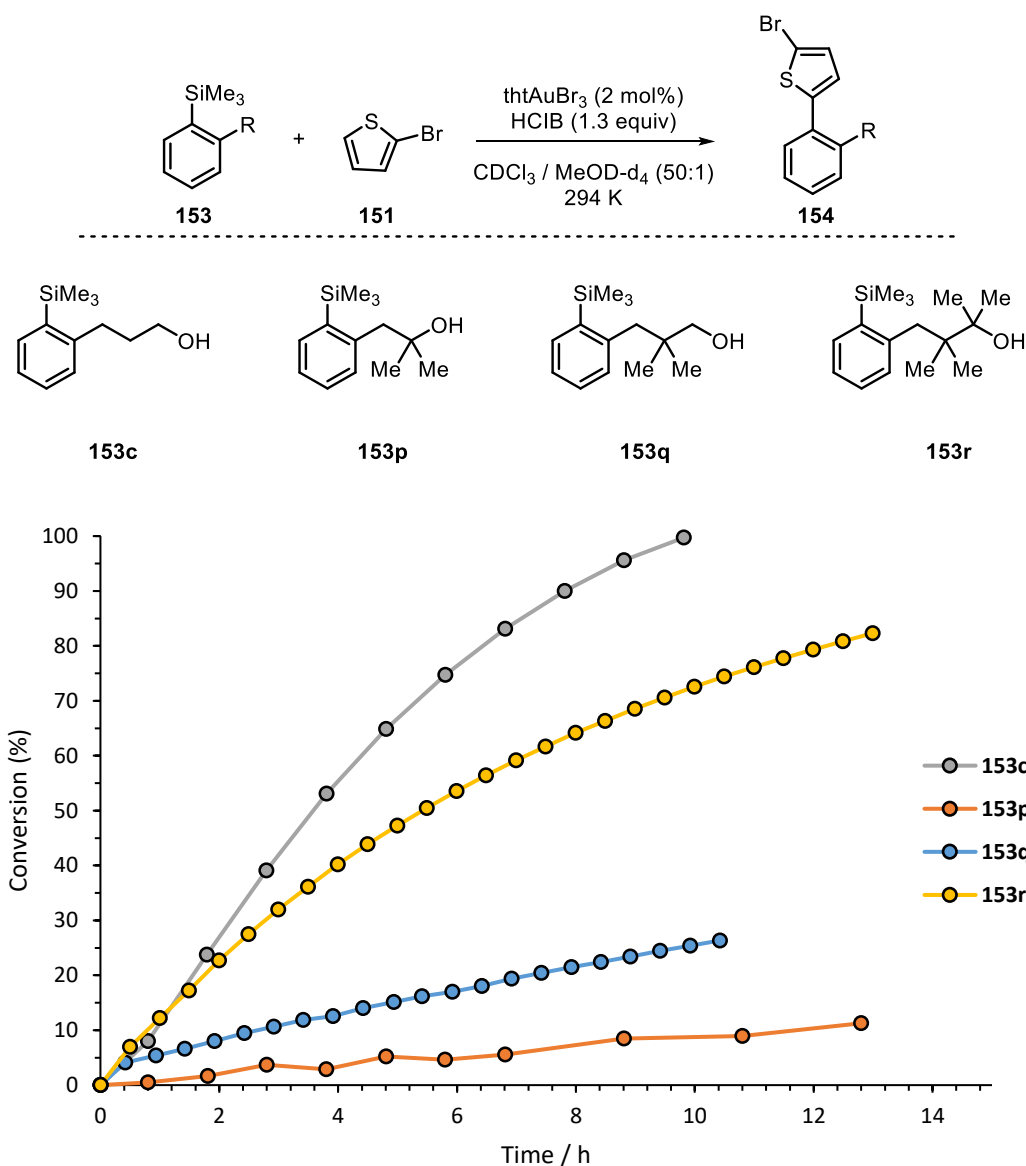
Increasing the molar equivalents of 2-bromothiophene prevented the reaction from stalling, resulting in increased reaction rates and complete consumption of the arylsilane (Figure 3.3). This would be consistent with a competing elimination prior to the second arylation event, whereby increasing the arene concentration prevents generation of the off-cycle species by increasing the rate of  $\pi$ -complexation.

The stability and conformation of the required metallocycle likely governs the reactivity of the substrate in arylation, as arene  $\pi$ -complexation is known to be turnover limiting for intermolecular coupling (Scheme 3.7). The nature of the tether (coordinating strength of the group) and its size (length as well as steric presence) could both be expected to have a significant impact on the rate of reaction, affecting both the position of the metallocycle-forming equilibrium ( $K_{eq}$ ) and the rate of coordination of the incoming arene ( $k_r$ ).



**Scheme 3.7.** Formation of a cyclometalated intermediate *en route* to arylation.

Consistent with this, varying the degree of substitution on the tether had a profound impact on the rate of reaction (Scheme 3.8).

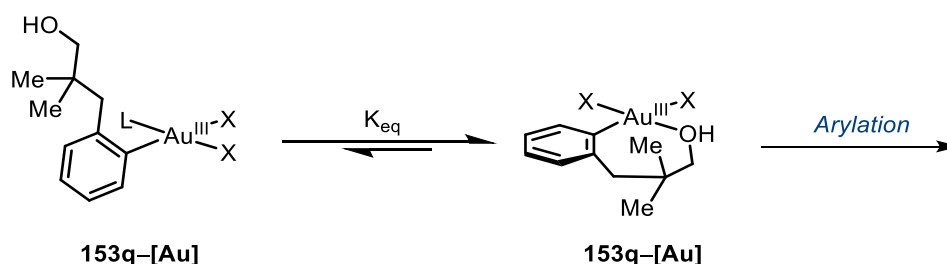


**Scheme 3.8.** Rate of coupling with 2-bromothiophene for arylsilanes **153c**, **153p**, **153q**, **153r**. [silane] = [arene] = 0.1 M.

The rate of arylation is dramatically suppressed for tertiary alcohol **153p**, reaching only 10% conversion in 12 hours. Efficient coordination to the metal centre is perhaps prevented in this case, causing the reactivity to more closely relate to that of the alkyl-substituted silanes discussed in Chapter 2.

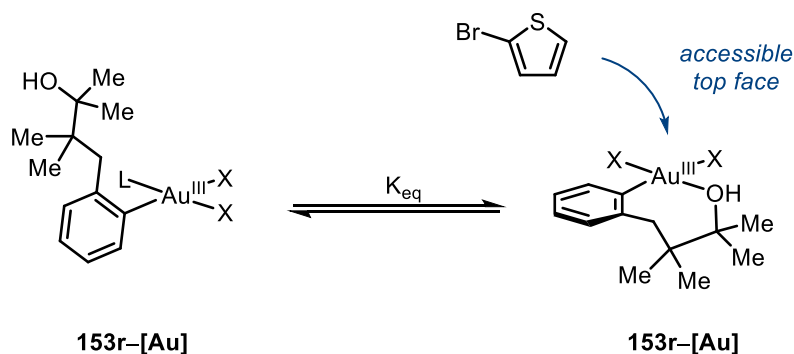
Considering the prevalence of the Thorpe-Ingold effect in organic reactivity,<sup>8</sup> the geminally-disubstituted methyl groups of silane **153q** might be expected to favour formation of the desired metallocycle (Scheme 3.9). Surprisingly though, the rate of arylation in this case is greatly reduced. While the kinetic stability of the intermediary metallocycle may be

improved, the conformation required for reactivity would likely direct the methyl substituents of the tether above and below the square planar arrangement. A blocking effect by these groups could explain the significant decrease in reactivity compared to the unsubstituted propanol tether (**153c**).



**Scheme 3.9.** Anticipated rate acceleration via Thorpe-Ingold effect (K).

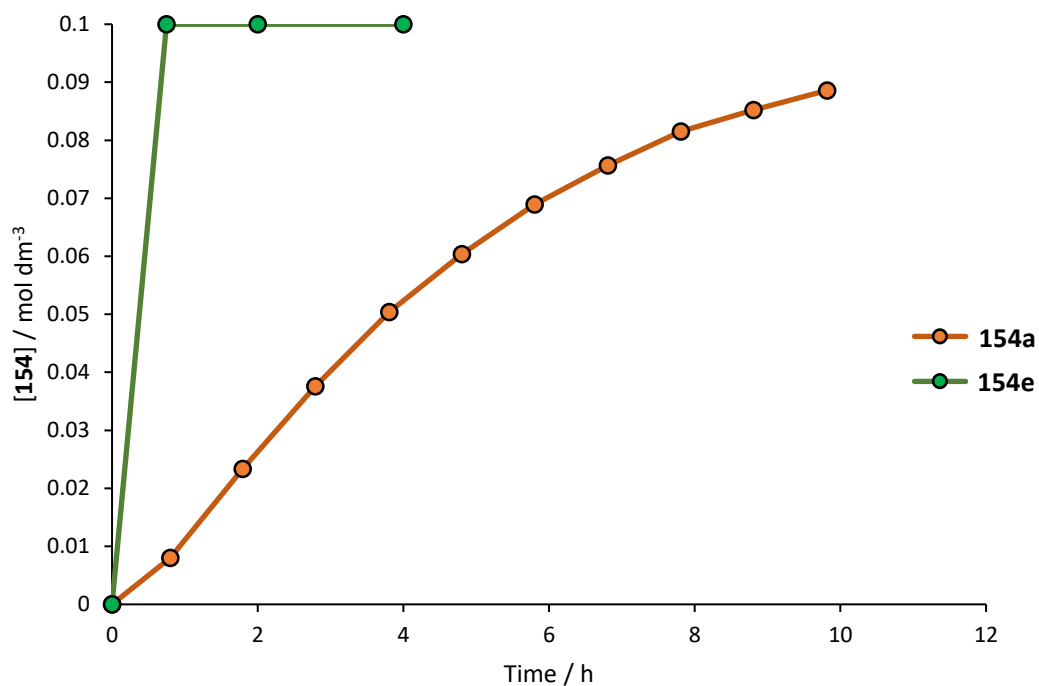
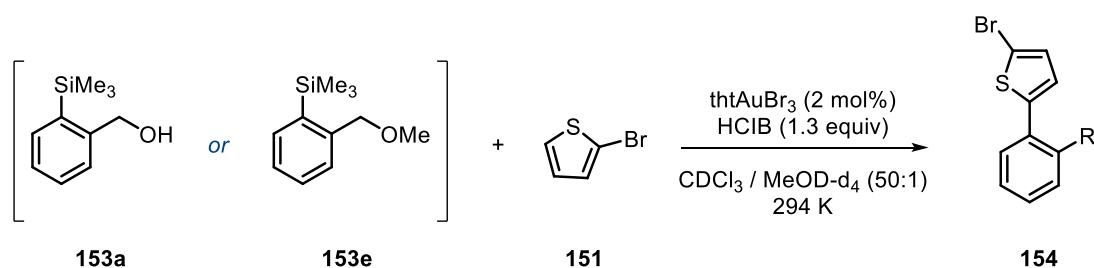
In marked contrast to these examples, the rate of arylation of silane **153r** is much closer to that of the unsubstituted linker, despite heavy substitution of the pendant chain. While the cause of this disparity in reactivity is not immediately clear, it is possible that the added substitution favours a metallocycle in which one face is left relatively accessible (Scheme 3.10). In both cases, accurately predicting the favoured conformation of the corresponding metallocycle is non-trivial given the ambiguity concerning bond lengths and angles at the gold-centre.



**Scheme 3.10.** Plausible explanation for the observed difference in reactivity.

### 3.2.2. Reactivity of Ether Tethers

Methyl ether containing tethers were also found to promote the arylation reaction, with a significantly faster rate of product formation (Scheme 3.11). The increase in reactivity is such that the coupling of **153e** with 2-bromothiophene was complete in less than 45 minutes (at 294 K).

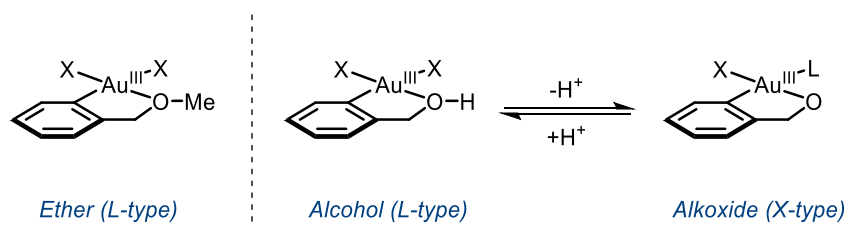


**Scheme 3.11.** Increased rate of arylation for methyl ether-containing substrate **153e**.

[silane] = [arene] = 0.1 M.

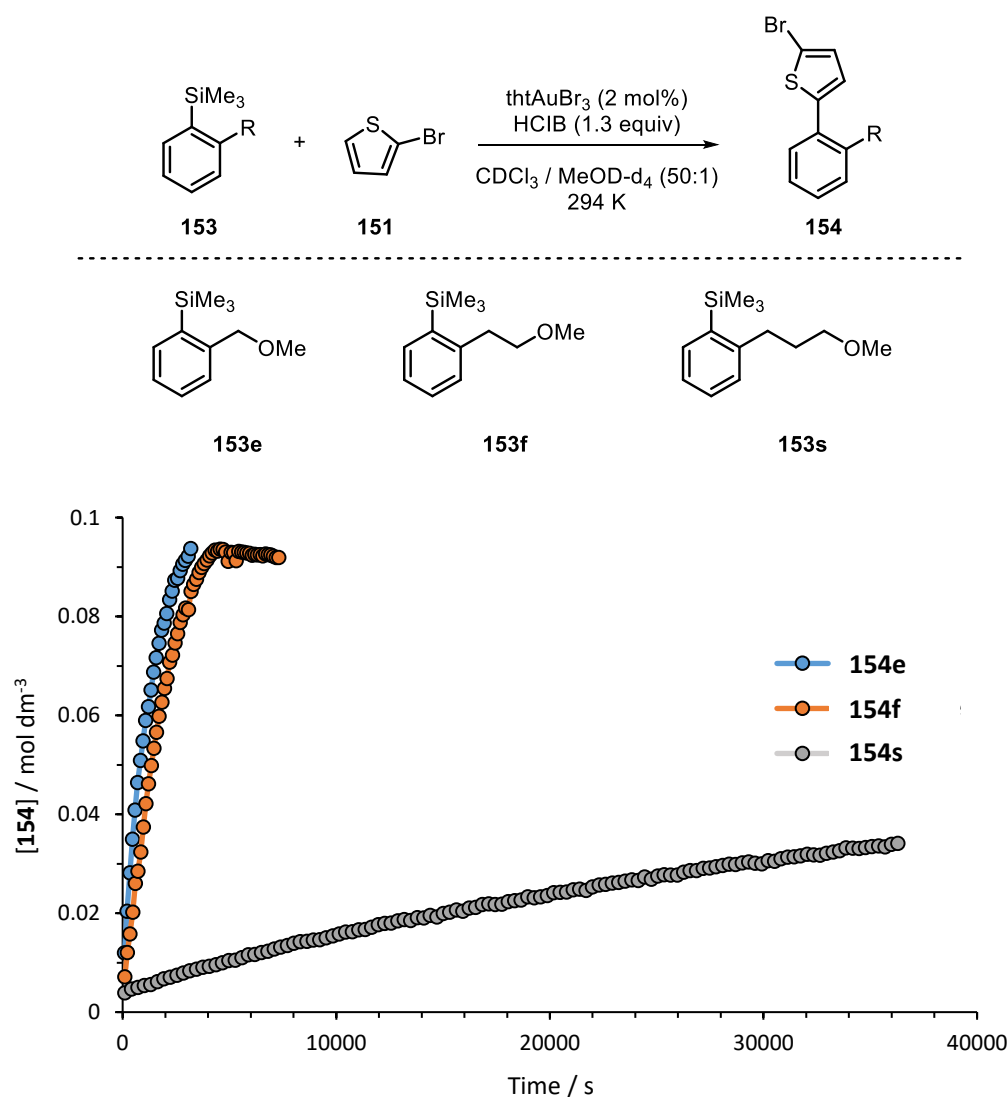
Once protected as the methyl ether, the coordinating tether is only able to act as a neutral  $2e^-$  (L-type) ligand. In contrast, two modes of coordination could be envisaged for the free alcohol; either as an analogous neutral (L-type) donor, or as an anionic (X-type) alkoxide ligand (Scheme 3.12). The marked difference in reactivity between the two substrates suggests that the activating effect is most effective with a neutral donor, and that a contribution from the anionic form is responsible for reducing the rate of reaction for substrates incorporating a free alcohol.





**Scheme 3.12.** Possible modes of coordination for ether- and alcohol-containing tethers.

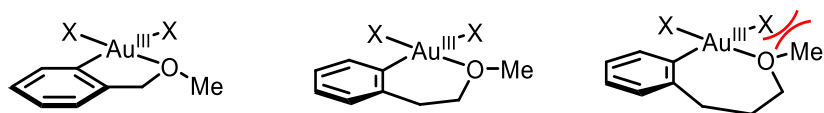
Arylsilanes **153e** and **153f** were found to have similar rates of arylation, with the ethanol derived tether no longer suffering from the stalling effect that was observed for the free alcohols (Scheme 3.13). However, adding an additional methylene unit to the tether caused a severe drop in reactivity.



**Scheme 3.13.** Effect of tether length on the reactivity of methyl ether substituents.

[silane] = [arene] = 0.1 M. Reaction monitored by *in situ* NMR.

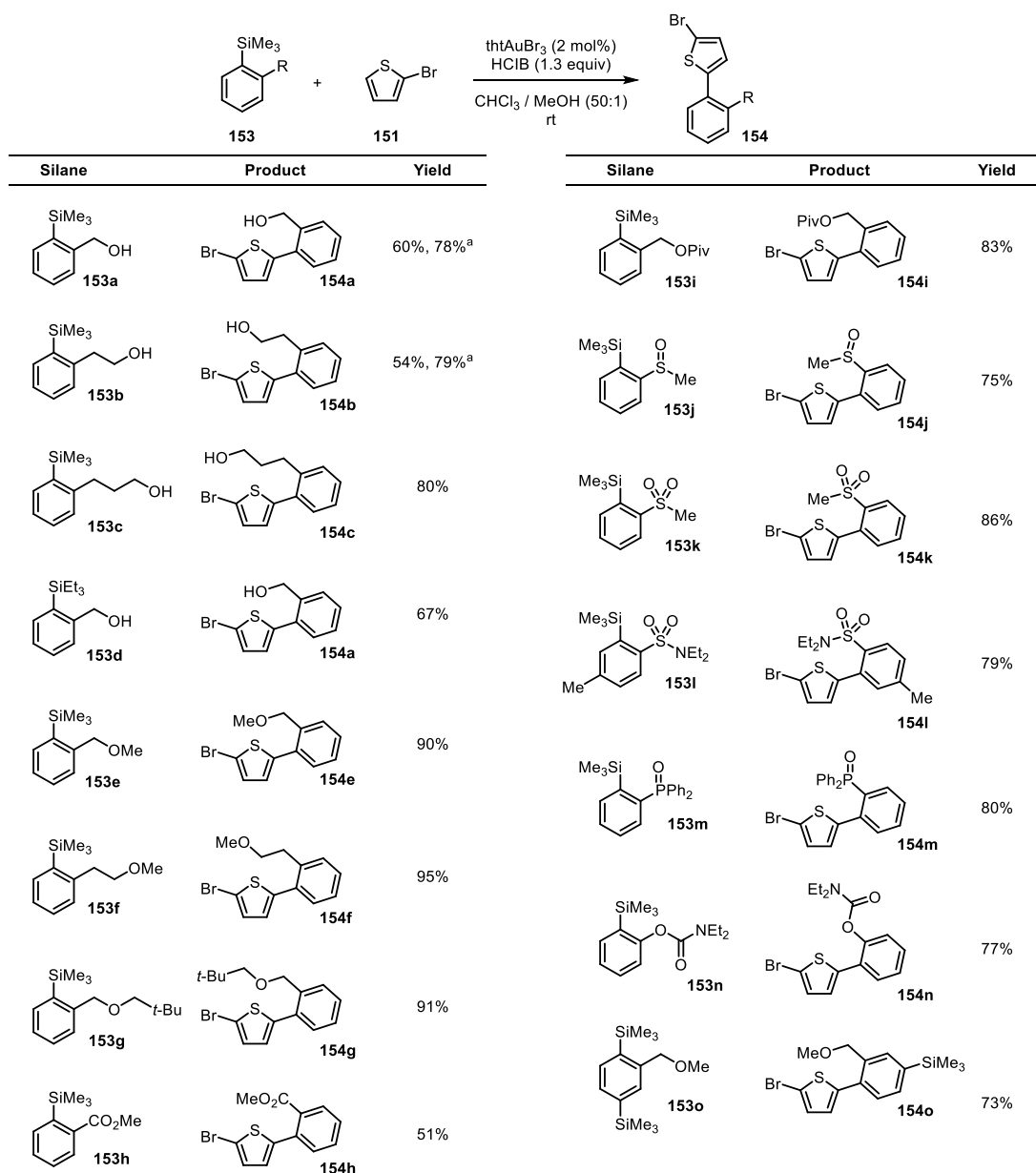
This is again attributed to the highly sensitive nature of the metal chelate, in which the direction of the terminal methyl group likely impacts both the stability and reactivity (Figure 3.4). While predicting the exact conformation of these intermediates is not straightforward, it is apparent that seemingly minor structural modifications to the arylsilane can have a profound impact on the rate of arylation; a feature that must be considered when designing suitable substrates for arylation.



**Figure 3.4.** Plausible reason for decrease in reactivity with increasing tether length.

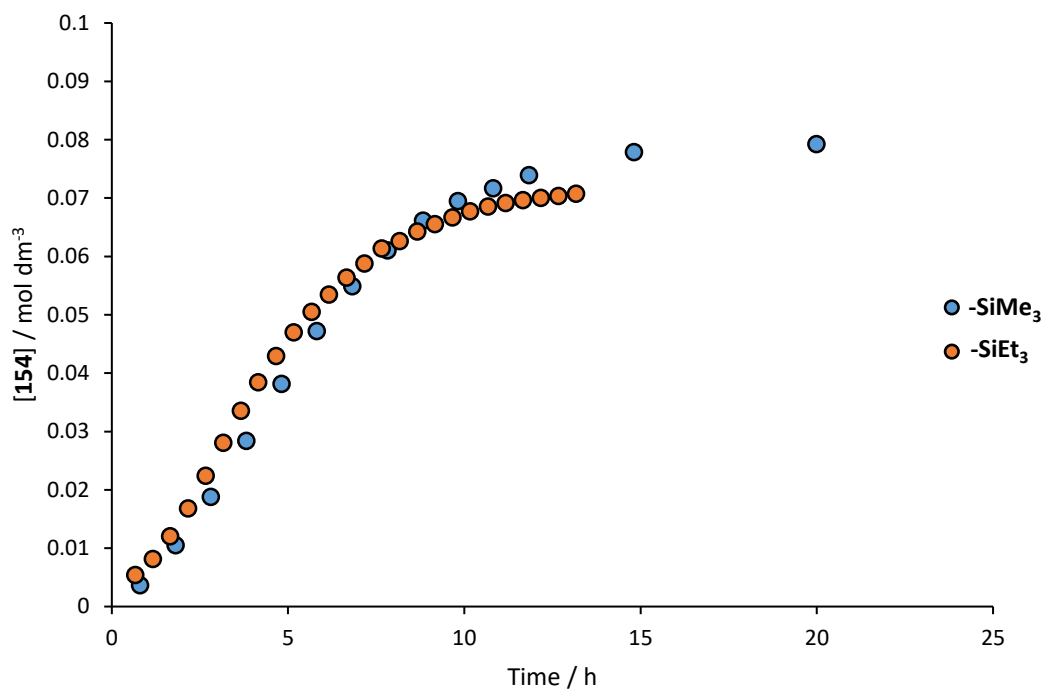
### 3.3. Preparative Arylation Reactions

Having demonstrated that pendant alcohols (and their methyl ether derivatives) were capable of promoting the arylation reaction, we speculated that other heteroatom-containing functional groups might also facilitate arylation. Pleasingly, a range of potentially-coordinating *ortho*-substituted arylsilanes proved to be effective coupling partners (Scheme 3.14). Preformed HCIB was employed as a stoichiometric oxidant in place of IBDA to avoid liberation of AcOH (which can undergo complicating transesterification with alcohols).



**Scheme 3.14.** Scope of the *ortho*-substituted arylsilane coupling partner. 1.0 mmol silane, 1.0 mmol arene. [a] 2 equiv arene; [b] 0.5 mmol scale.

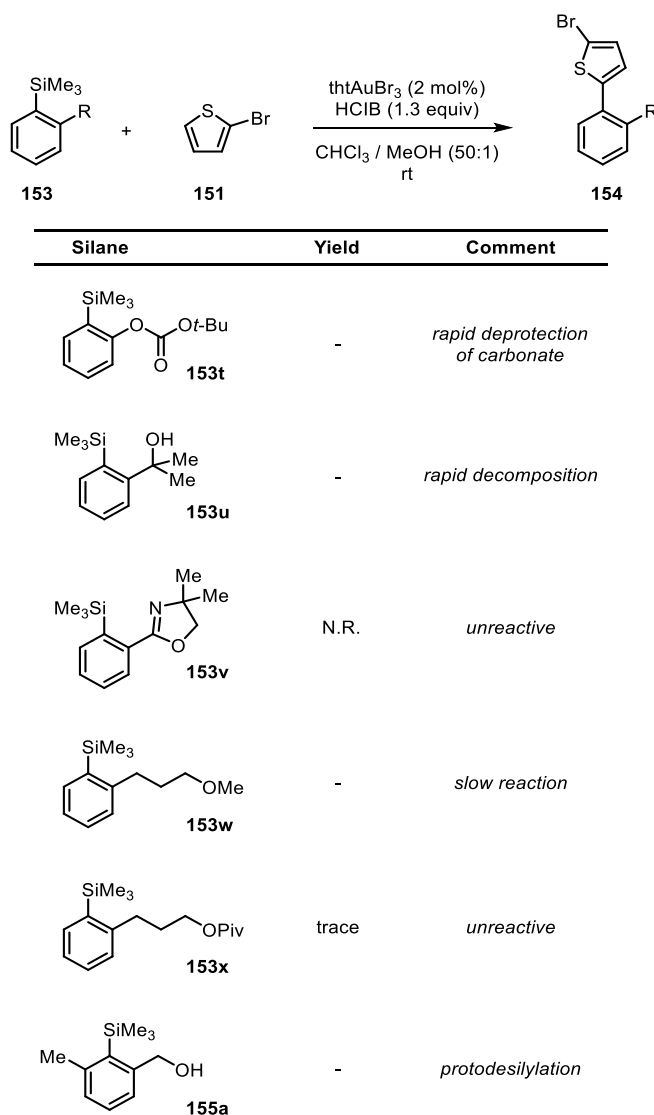
Arylsilanes possessing tethered alcohols could be cleanly arylated at room temperature, with a slight improvement in yield when employing an excess of the arene (**153a-c**). Interestingly, a triethylsilane analogue (**153d**) could be coupled under the reaction conditions, benefitting from the activating effect of *ortho*-substitution in transmetalation. The reaction profile almost perfectly overlays with the corresponding trimethylsilane, suggesting that the turnover-limiting step is the same in both cases (Figure 3.5).



**Figure 3.5.** Comparison of reaction profiles for TMS and TES substrates. Reaction monitored by *in situ* NMR at 294 K.

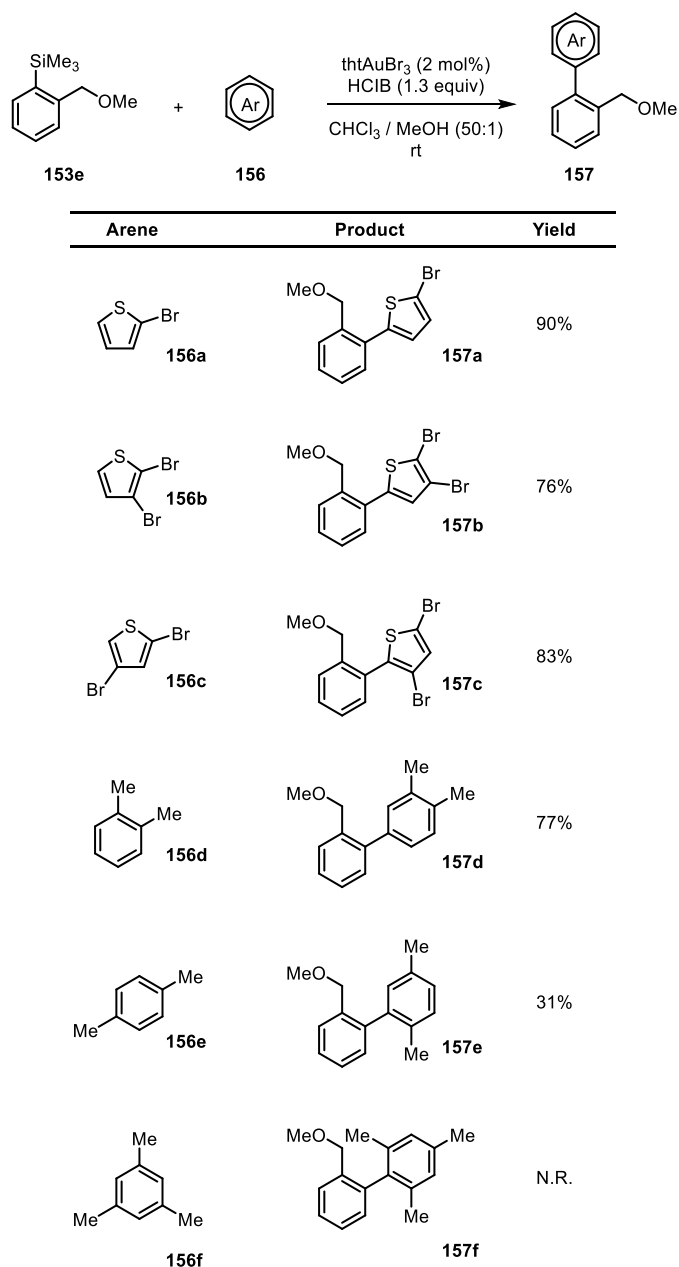
Methyl ethers proved suitable coordinating substituents (**153e,f**), as well as the more sterically imposing neopentyl ether (**153g**). Esters (**153h,i**), sulfur-containing functional groups (**153j-l**), and phosphine oxides (**153m**) could all be arylated in good yield. When two silyl groups are present in the substrate there is completely selective coupling at the *ortho*-substituted position; the alternative regioisomer could not be detected (**153o**).<sup>xvi</sup>

<sup>xvi</sup> Near complete regioselectivity for *ortho*-substituted arylsilanes has also been observed in other electrophilic desilylation reactions.<sup>67,68</sup>



**Scheme 3.15.** Summary of *ortho*-substituted arylsilanes that could not be effectively arylated.

A number of *ortho*-substituents proved unsuitable for use in the arylation reaction. Acid-sensitive functional groups, such as Boc-protected phenol derivative (**153t**), can undergo facile deprotection in the presence of sulfonic acids. Tertiary benzylic alcohol (**153u**) underwent rapid conversion to an unidentified, but catalytically unreactive by-product (presumably *via* dehydration). The dimethyloxazoline substituent (**153v**) was unable to promote the desired coupling reaction, resulting in complete recovery of starting material. Unlike the protected benzyl alcohols **153e** and **153i**, longer chained alcohol derivatives **153w** and **153x**, were either impractically slow or unreactive (more forcing conditions were not tested). 2,6-Disubstituted arylsilane **155a** suffered from a reduced rate of reaction that was compounded by competing protodesilylation (see Section 3.31).

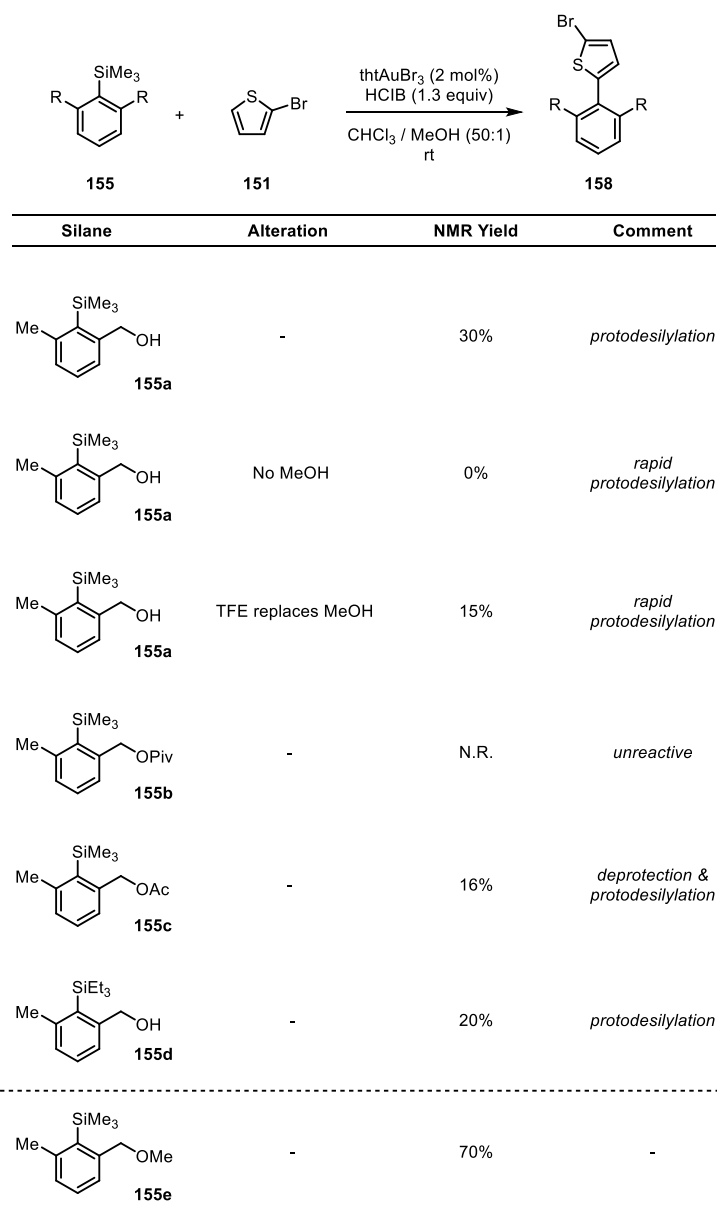


**Scheme 3.16.** Selection of arenes that can be used in the arylation reaction of *ortho*-substituted arylsilanes.

The scope of arene partners that can be used appears to be similar to the original methodology (based on the limited selection tested),<sup>1</sup> though tolerance for *ortho*-substitution of the arene partner is significantly reduced (**156e,f**).

### 3.3.1. 2,6-Disubstituted Arylsilanes

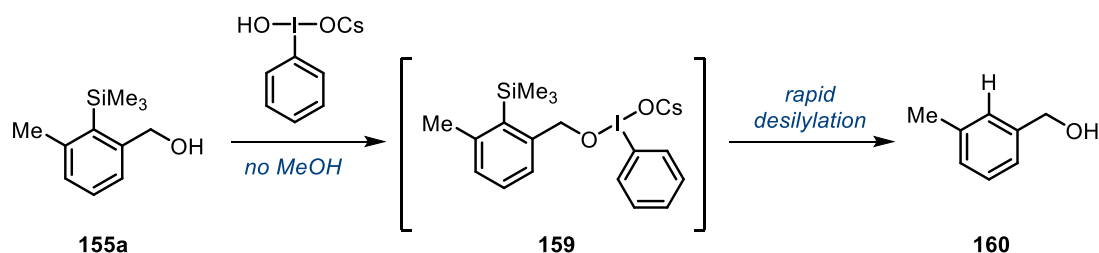
The fact that 2,6-disubstituted arylsilane **155a** undergoes a competing desilylation reaction is perhaps unsurprising given the known reactivity of these substrates in protodesilylation and related reactions (see Section 2.12). However, evidence that arylation was also possible suggested that modification of the arylsilane reagent or the reaction conditions might enable successful coupling. Suppression of the protodesilylation pathway, or acceleration of the desired arylation (or a combination of both), should lead to an increase in product yield.



**Scheme 3.17.** Attempted arylation of 2,6-disubstituted arylsilanes.<sup>xvii</sup>

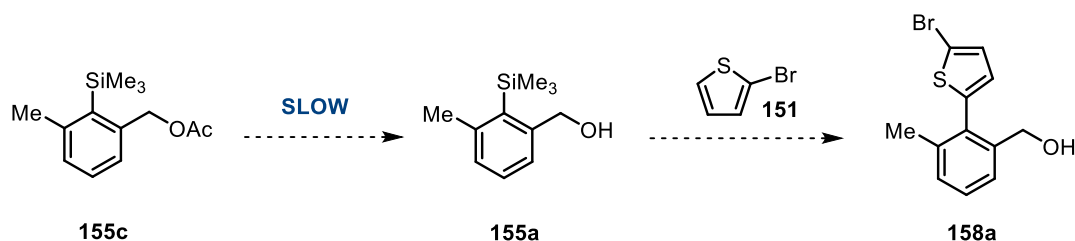
<sup>xvii</sup> NMR yields estimated based on the conversion of 2-bromothiophene using signal at  $\delta = 6.61$  ppm

Using the standard reaction conditions, the arylated product could be observed in approximately 30% yield (by  $^1\text{H}$  NMR), with the remaining arylsilane consumed by protodesilylation (Scheme 3.17). Removing the methanol co-solvent, anticipated to increase the rate of the desired arylation reaction, resulted in rapid protodesilylation (full consumption of arylsilane within 15 minutes). Replacing methanol with the less strongly coordinating trifluoroethanol, known to accelerate the rate of intermolecular arylation,<sup>9</sup> again led to fast desilylation. It is possible that under these conditions complexation to the iodine(III) reagent occurs, activating the substrate to protodesilylation (Scheme 3.18).



**Scheme 3.18.** Possible explanation for accelerated rate of desilylation in the absence of methanol.

Protecting the alcohol as a pivaloyl ester successfully prevented the undesired desilylation of the substrate to any significant extent, but also prevented the arylation reaction (**155b**). We envisaged that protecting the alcohol as an acetate may prevent protodesilylation, but allow slow release of the alcohol to enable coupling to take place (Scheme 3.19).



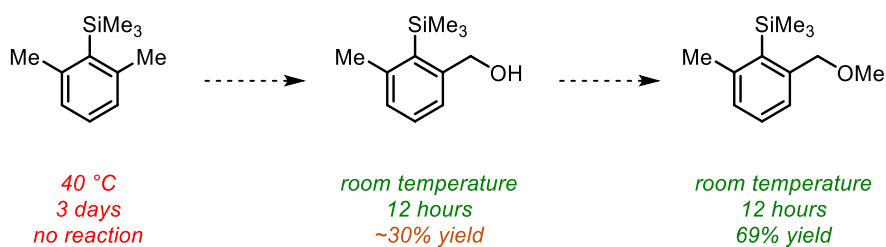
**Scheme 3.19.** Proposed slow release strategy to maintain a low concentration of **155a** in solution.

Unfortunately, this led to a decrease the yield of the arylated product (**155c**). The liberation of CSA throughout the course of the reaction accelerates the rate at which the deprotection occurs, resulting in accumulation of the free alcohol, and a significant amount of observed desilylation. Aryltriethylsilanes ( $\text{Ar-SiEt}_3$ ) are typically less reactive than their trimethyl counterparts in desilylative reactions, and are therefore slightly more stable under acidic



conditions.<sup>10,11</sup> However, the use of triethylsilane **155d** did not lead to any improvement in the arylation reaction.

However, protecting the alcohol as a methyl ether proved effective (**155e**), facilitating the desired coupling while significantly suppressing the rate of protodesilylation. Performing the reaction on a preparative scale afforded the arylated product in 69% yield.<sup>xviii</sup> This represents a significant result given the complete lack of reactivity exhibited by other heavily substituted arylsilanes in direct arylation (Figure 3.6).



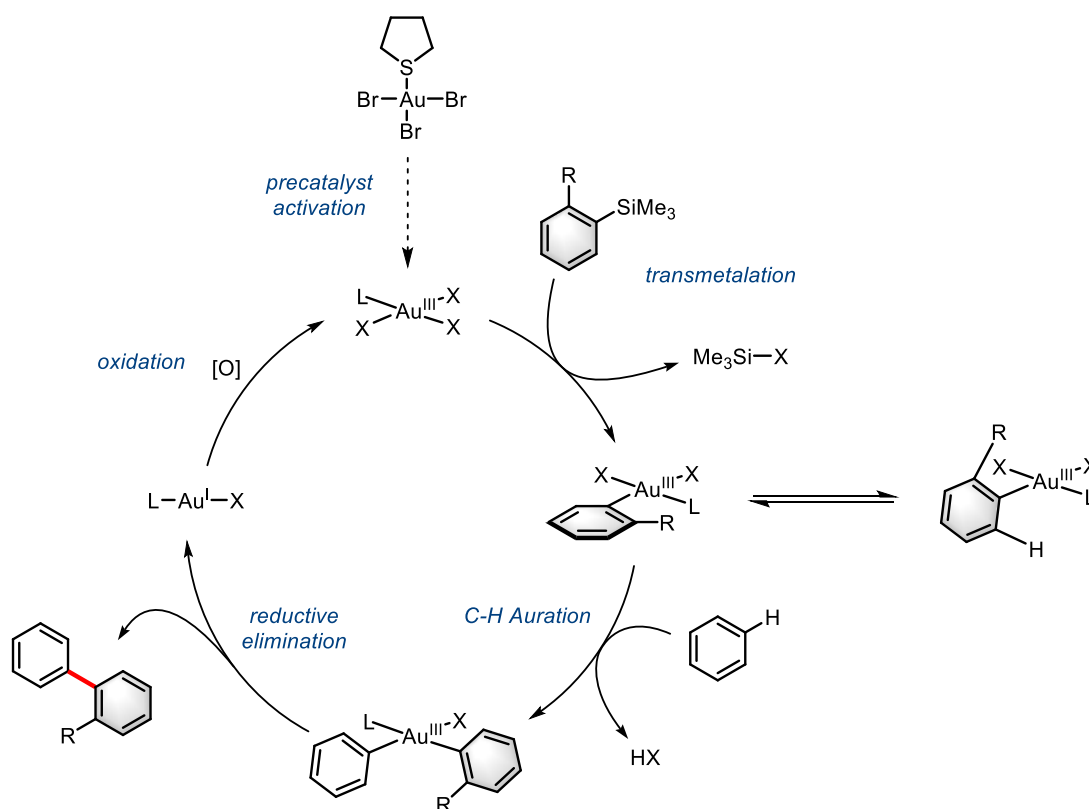
**Figure 3.6.** Modification of arylsilane reagents to allow arylation of 2,6-disubstituted substrates at room temperature.

<sup>xviii</sup> Purity estimated to be ~90% (by <sup>1</sup>H NMR)

### 3.4. Summary

Arylsilanes bearing *ortho*-substitution were previously thought to be unreactive in gold-catalysed arylation, as well as in related reactions.<sup>12,13</sup> While this may be true for simple alkyl substituents, we have identified that incorporation of a suitable coordinating group to the substrate can allow the desired reaction to proceed. A range of different functional groups are effective in this regard, and the arylated products can typically be obtained in good yield. Even the arylation of a severely hindered 2,6-disubstituted arylsilane could be enabled by incorporation of a pendant ether.

In contrast to the previously reported mechanistic study, in which the nature of the arylsilane reagent was found to have little impact on the rate of reaction,<sup>14</sup> the relative reactivity of these substrates covers a broad range. This is attributed to the importance of a key intermediate of the catalytic cycle, in which formation of a metallocycle is required to generate a reactive conformation for arylation (Scheme 3.20). Based on this proposed intermediate, it is apparent that structural or electronic changes to the substrate can have a profound effect on the overall reactivity.



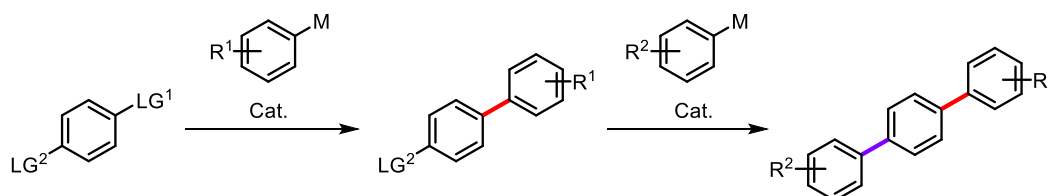
**Scheme 3.20.** Adapted catalytic cycle to include the proposed conformational requirement prior to C–H auration.

Of all the functional groups tested, short-chained methyl ethers proved most effective, resulting in reliably high yields and fast rates of arylation. The compatibility of other ether-containing functional groups has not been examined in detail, and it is appreciated that the identification of a more readily cleaved alternative would be more synthetically useful (*e.g.*, a –MOM protected alcohol).

## 3.5. Future Work

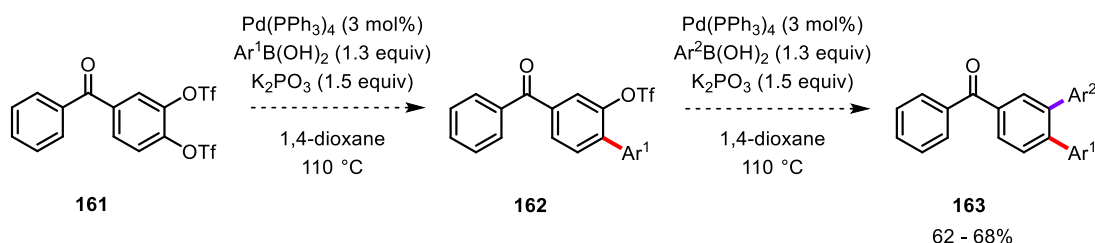
### 3.5.1. Sequential Arylation

Sequential couplings, carried out by the same or a different catalyst species, are an attractive method to construct multiple bonds in one step, provided that selectivity can be effectively controlled (Scheme 3.21).<sup>15–17</sup> Avoiding the need to isolate and purify an intermediate can be a significant benefit to the processing time and cost of a synthesis, particularly on large-scale.



**Scheme 3.21.** Typical method for sequential coupling using different leaving groups.

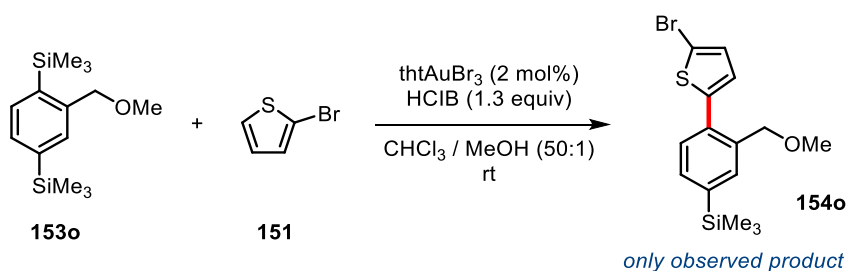
Most sequential methods derive chemoselectivity from the use of leaving groups that possess intrinsically different reactivity,<sup>xix</sup> such as the aryl (*pseudo*)halides in palladium catalysis.<sup>18,19</sup> However, it is also possible to differentiate between identical leaving groups based on steric and/or electronic discrimination. For example, Langer and co-workers described a palladium-catalysed coupling in which two triflates were sequentially cross-coupled due to electron-withdrawing effects (Scheme 3.22).<sup>20</sup>



**Scheme 3.22.** Langer's sequential Suzuki-Miyaura coupling of electronically differentiated aryl triflates.

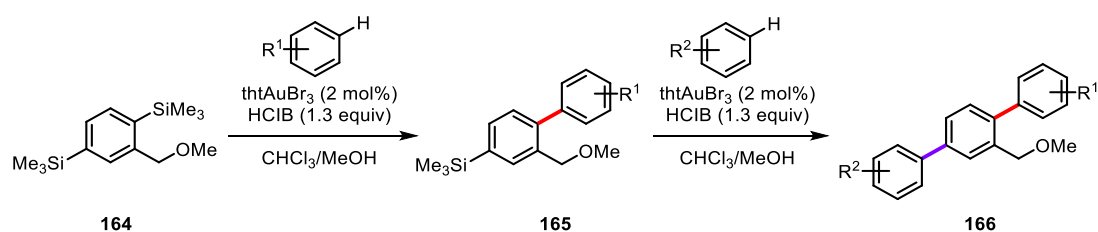
Arylsilane **153o**, which contains two (identical) competing silyl groups was found to undergo selective coupling at one site due to the activating effect of *ortho*-substitution (Scheme 3.23).

<sup>xix</sup> The use of different silyl groups to allow sequential coupling under palladium catalysis has been reported by Denmark and co-workers.<sup>69</sup>



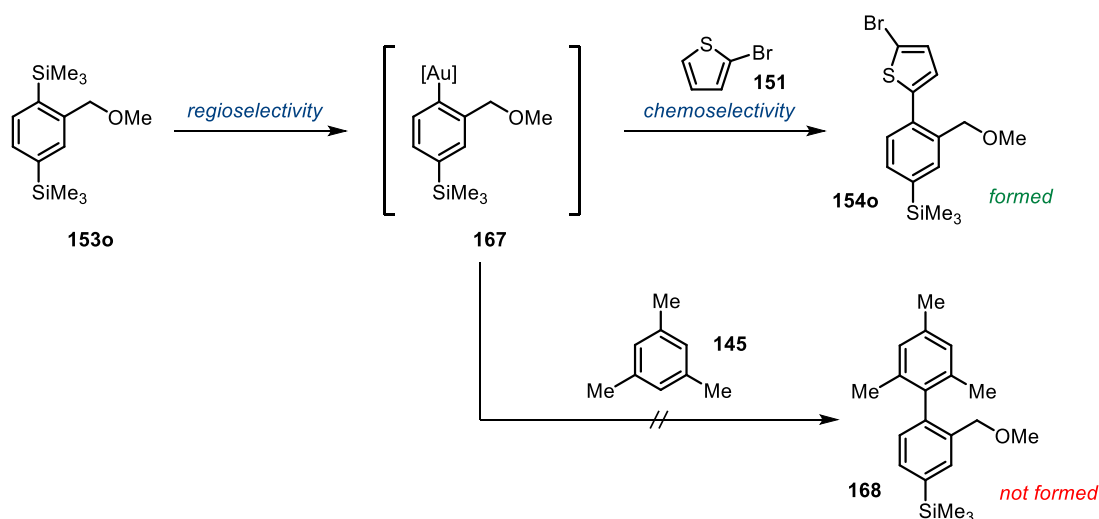
**Scheme 3.23.** Selectivity for *ortho*-substituted TMS group in arylation.

This highlighted the potential for *ortho*-substituted silanes to be used in sequential couplings, with regioselectivity dictated by the degree of neighbouring substitution of both silyl groups. Stepwise addition of two arene coupling partners could then provide the required control over both arylation events, resulting in the formation of a single product (Scheme 3.24).



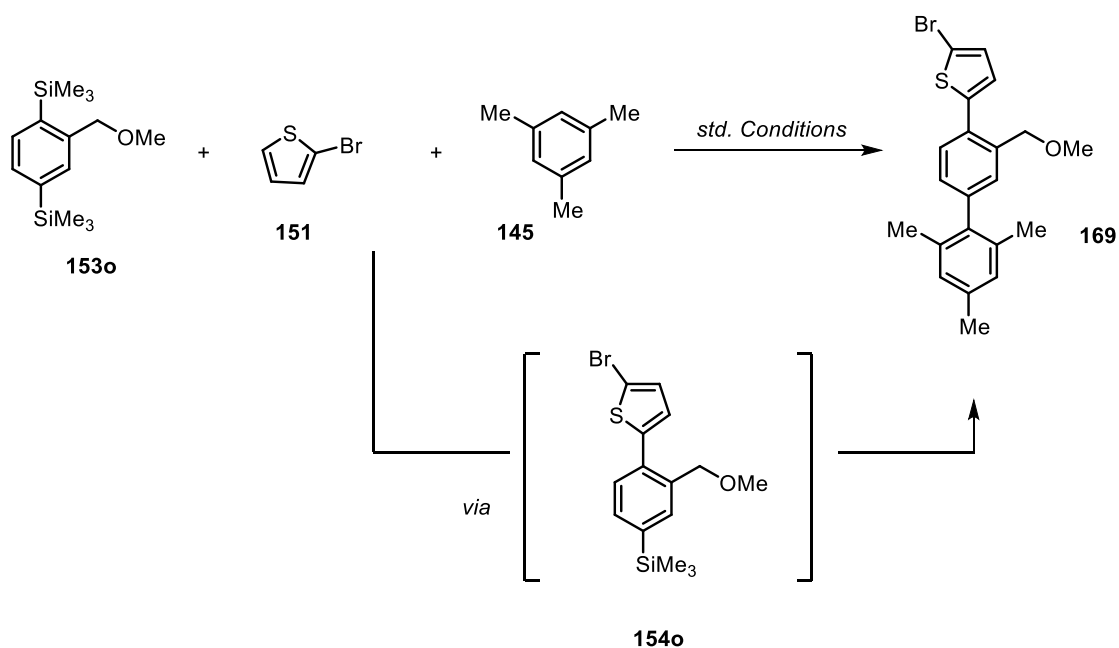
**Scheme 3.24.** Proposed method for sequential arylation with selectivity governed by the reactivity of the silyl groups.

In addition to discrimination between the two silyl groups at the transmetalation step, the incompatibility of *ortho*-substitution on both coupling partners offers the possibility of selectivity at the C–H auration step of the catalytic cycle (Scheme 3.25). Intermediate **167** is unable to undergo reaction with sterically hindered arenes and so will selectively react with the less substituted substrate, even if it is less electronically activated. Only during the second coupling, in which the arylsilane has no neighbouring substituent, will the arylation with the hindered arene take place.



**Scheme 3.25.** Chemoselectivity derived from the incompatibility of *ortho*-substituents on both coupling partners.

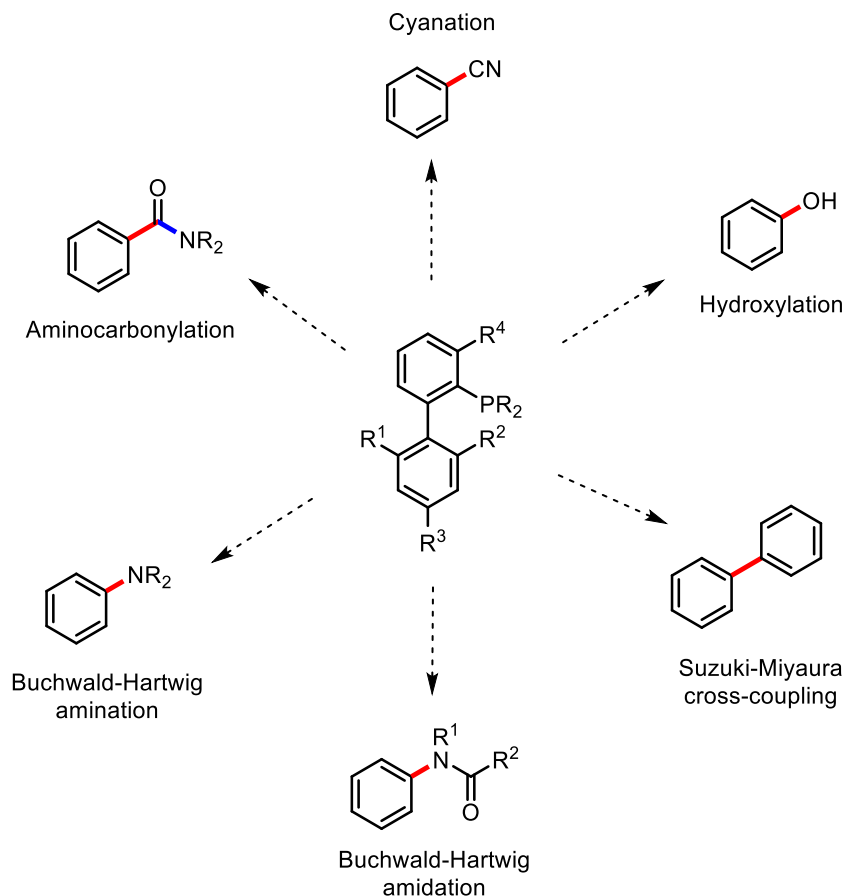
Therefore, it should be possible to perform a sequential coupling with all components present from the outset, to generate a single product with good control over selectivity (Scheme 3.26).



**Scheme 3.26.** Proposed sequential coupling to form a single product from a mixture of starting reagents.

### 3.5.2. Phosphine Ligand Synthesis

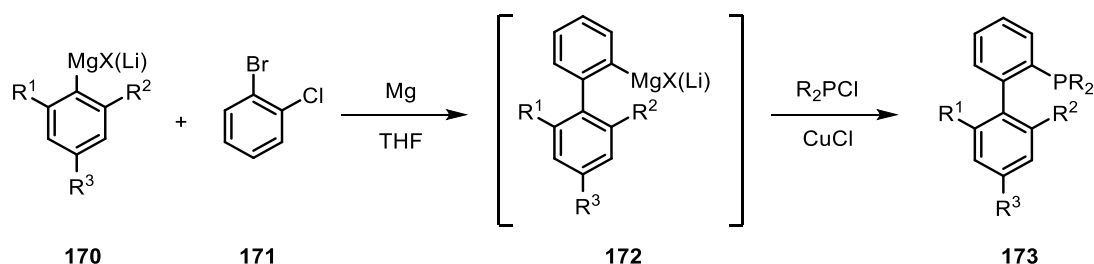
Buchwald phosphine ligands, used either in a free unprotected form or as palladacycle based pre-catalysts, enjoy a prominent status in modern day cross-coupling.<sup>21</sup> Noteworthy applications feature state-of-the-art methodologies for Suzuki-Miyaura,<sup>22,23</sup> and Negishi cross-coupling reactions,<sup>24–27</sup> Buchwald-Hartwig amination,<sup>28–32</sup> amidation,<sup>33,34</sup> and the cyanation,<sup>35–37</sup> hydroxylation,<sup>38</sup> and aminocarbonylation<sup>39</sup> of aryl halides (Figure 3.7). Most of the ligands share a common biaryl scaffold, with key features that can be modified to tailor the reactivity of the metal complex to different applications.



**Figure 3.7.** Overview of some applications of biaryl phosphine ligands in palladium catalysis.

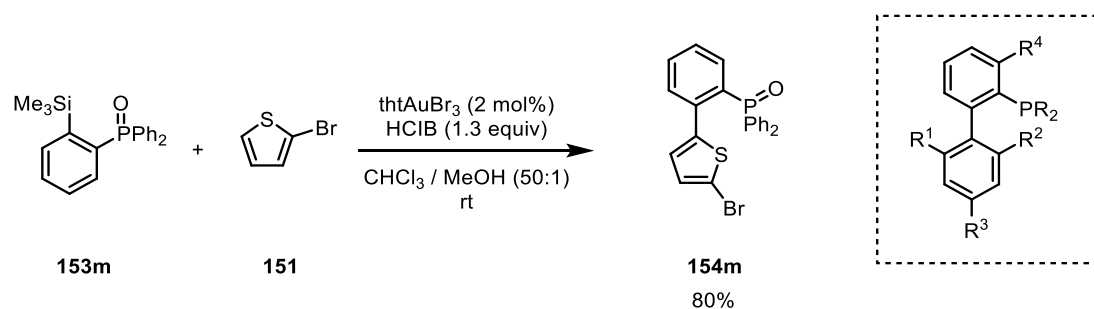
The ligands are most commonly synthesised in a one-pot procedure, combining an aryl Grignard, *in situ* generated benzyne, and chlorophosphine to generate the biaryl phosphine in moderate yield (Scheme 3.27).<sup>40</sup> The products exhibit surprising air stability, and can typically be purified by routine recrystallisation. However, one caveat to this method is the requirement to introduce the second aryl group as an organolithium or Grignard reagent, limiting the choice

of functionalities that can be incorporated. In addition, the bis-alkyl chlorophosphine reagents used are often pyrophoric, necessitating careful handling under an inert atmosphere.



**Scheme 3.27.** Established route for the synthesis of biaryl phosphine ligands.

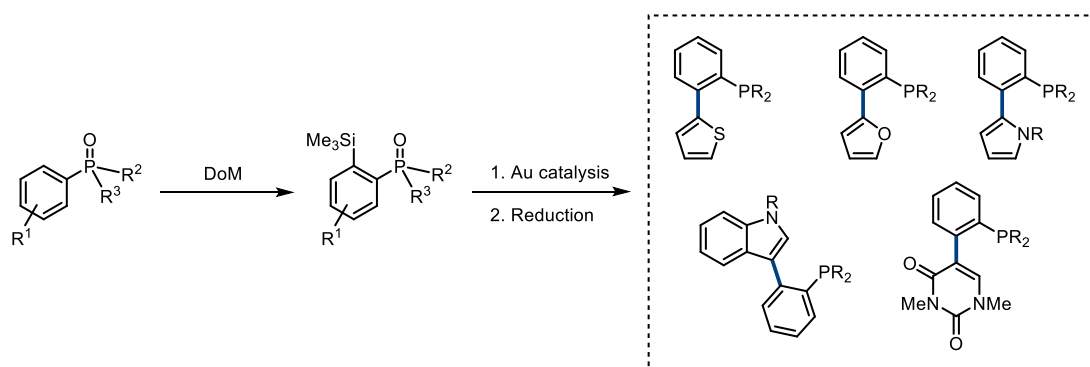
Phosphine oxide containing arylsilane **153m** has been demonstrated to be a competent coupling partner in the gold-catalysed arylation reaction of 2-bromothiophene (Scheme 3.28). The product of coupling, if reduced to the free phosphine, contains the same basic scaffold as the aforementioned Buchwald ligands, but differs in that it contains a heteroarene as the second aryl unit.



**Scheme 3.28.** Arylation of silane **153m** to form biarylphosphine oxide **154m**.

Based on the established substrate scope of the gold-catalysed coupling, this aromatic group could be varied to incorporate a range of sterically and electronically diverse heteroarenes (Scheme 3.29). These may constitute a class of hemi-labile ligands with diverse properties and potential applications, able to coordinate to metals either through the  $\pi$ -system, or the lone pair(s) of the heteroatom.



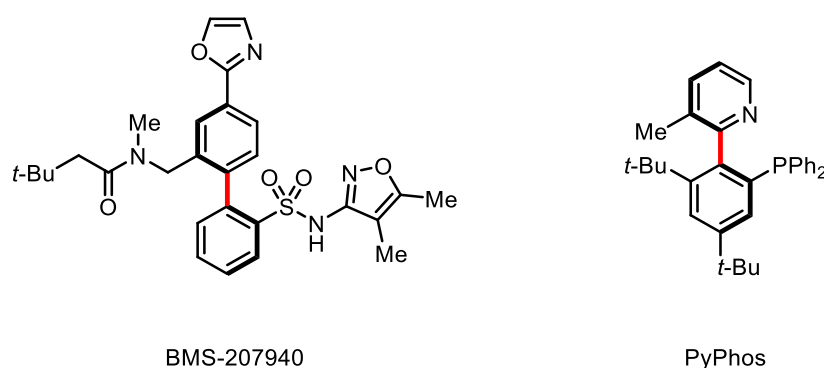


**Scheme 3.29.** Proposed synthetic route to access a range of diverse phosphine ligands from one common starting material.

While modifications to the common biaryl scaffold have been extensively examined, the incorporation of (substituted) heteroarenes into the ligand structure is less well studied (especially for alkyl phosphines).<sup>41–44</sup> This is perhaps due to the required linear synthetic route that prevents facile diversification. In contrast, synthesis of a small number of arylsilane precursors could allow for rapid generation of an entirely novel phosphine ligand library.

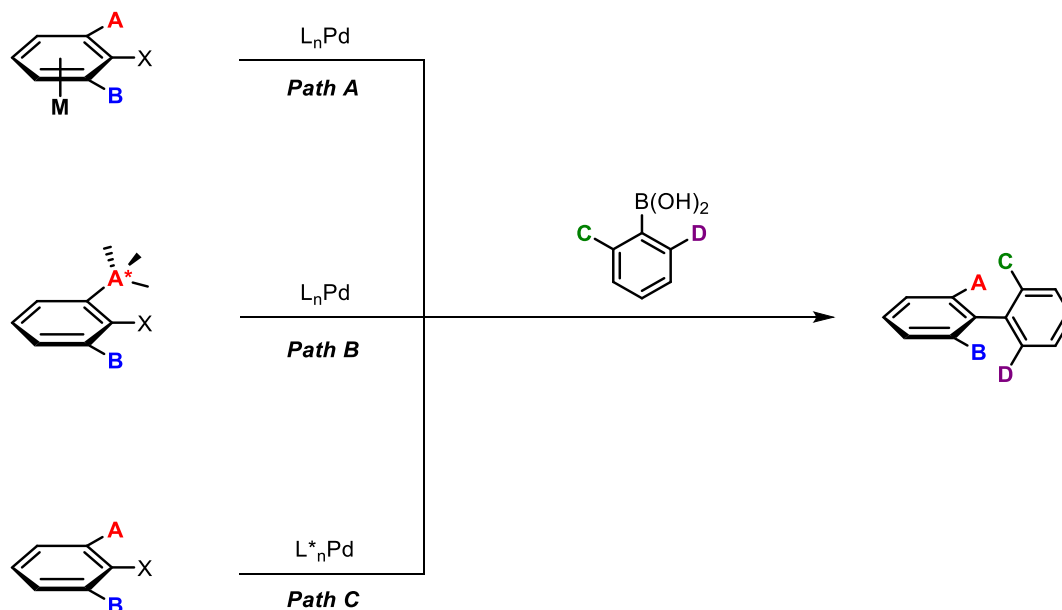
### 3.5.3. Chiral Biaryls

The selective synthesis of atropisomerically pure biaryl compounds is a significant challenge in modern transition metal catalysis. As a common structural motif in natural products,<sup>45</sup> active pharmaceutical ingredients,<sup>46–48</sup> and in chiral ligand structures,<sup>49</sup> a mild and general method for their synthesis is highly sought after.



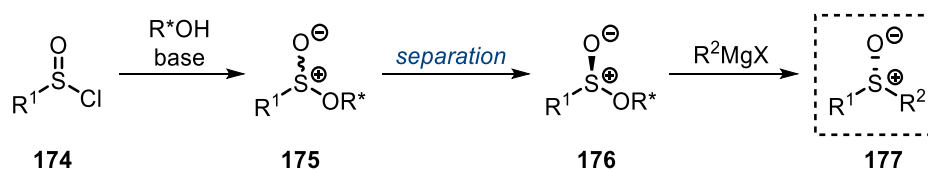
**Figure 3.8.** Endothelin receptor antagonist BMS-207940,<sup>50</sup> and axially chiral ligand PyPhos.<sup>51</sup>

The most commonly utilised method in the literature relies on an asymmetric Suzuki-Miyaura cross-coupling, in which chirality is either transferred from the substrate (Path A or B) or from the catalyst (Path C) to form a single atropisomer as the product (Scheme 3.30).<sup>52,53</sup>



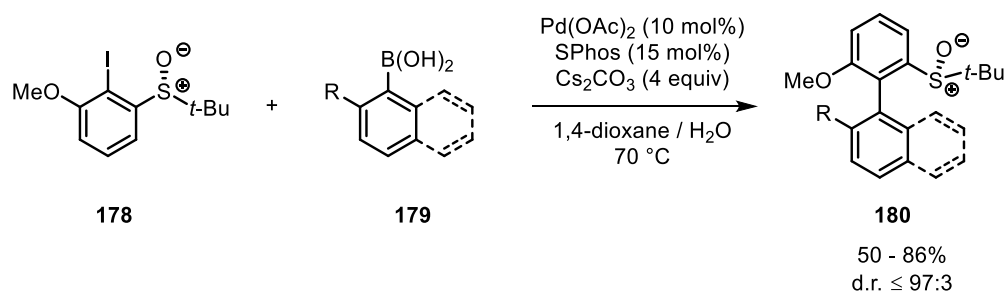
**Scheme 3.30.** Different strategies to perform asymmetric Suzuki-Miyaura couplings.

Chiral sulfoxides are an established class of ligand used to effect a variety of transition metal-catalysed asymmetric transformations.<sup>54,55</sup> They can be reliably synthesised in a method pioneered by Andersen and co-workers, in which a sulfinyl chloride is reacted with a chiral alcohol to produce diastereomeric sulfinate esters; these can then be separated by crystallisation or chromatography. Treatment of one diastereomer with an organometallic reagent results in alkylation with inversion of stereochemistry to yield an enantiomerically pure sulfoxide (Scheme 3.31).<sup>56–59</sup>



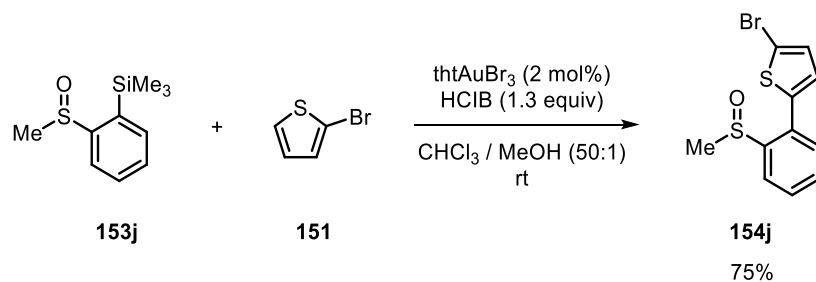
**Scheme 3.31.** Andersen's method of chiral sulfoxide synthesis using an alcohol auxiliary.

Aryl iodides containing a chiral sulfoxide auxiliary have been utilised by Colobert, Fernández, Khiar, and their respective co-workers, to enable a diastereoselective Suzuki-Miyaura coupling (Scheme 3.32).<sup>60</sup> The axially chiral products can be obtained in good yield and diastereomeric purity, using fairly typical conditions for palladium catalysis.

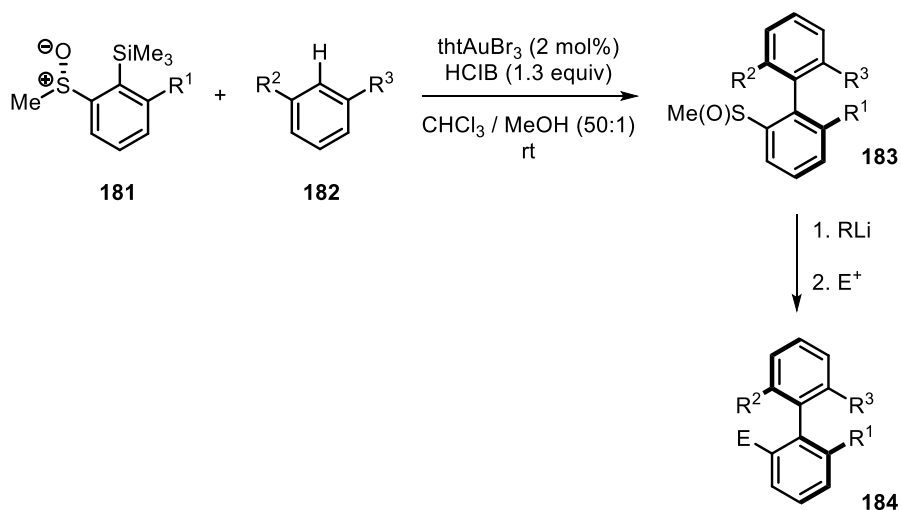


**Scheme 3.32.** Asymmetric Suzuki-Miyaura coupling using a chiral sulfoxide auxiliary.

The fact that arylsilane **153j** is a competent coupling partner in gold-catalysed direct arylation provides an opportunity for the development of a complementary diastereoselective biaryl synthesis (Scheme 3.33). A room temperature coupling offers the possibility to synthesise biaryls that are more prone to thermal racemisation. Following arylation, the sulfoxide directing group can be removed or modified *via* established methods of lithium-sulfoxide exchange (Scheme 3.34).<sup>61-65</sup>



**Scheme 3.33.** Arylation of **153j**, containing an *ortho*-sulfoxide group.



**Scheme 3.34.** Proposed synthesis of axially chiral biaryls via gold-catalysed direct arylation.

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**Catch and Release Catalysis**

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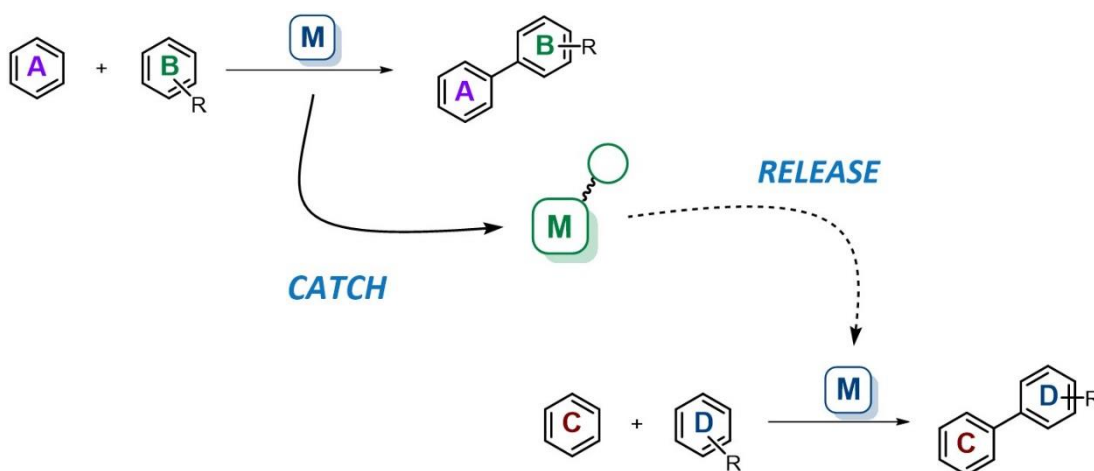
## 4.1. Introduction

The effective recovery and reuse of transition metal catalysts represents a longstanding challenge throughout applied industrial chemistry.<sup>1</sup> Not only does the ability (or inability) to recycle a catalyst on large-scale have significant financial implications, but often purification requirements stipulate that levels of trace metal contaminants must fall within certain levels. This is particularly pertinent in the pharmaceutical industry, where regulatory bodies demand very tight control over the quantity of metals allowed in final active pharmaceutical ingredients (APIs). As a late transition metal, gold is subject to fairly strict regulations; FDA oral permitted daily exposure limit (PDE) = 100 mg/day.<sup>2</sup> Therefore, for a gold-catalysed reaction to be amenable to industrial scale-up, there must be a method in place to ensure that the catalyst is effectively purified from the final product.

The most convenient methods used in process chemistry to remove metal contaminants are recrystallisation, aqueous washing, and distillation.<sup>3–5</sup> These processes tend to work relatively well for systems in which the metal is unlikely to be strongly bound to the product (compounds without coordinating functional groups). Unfortunately, the very nature of pharmaceutical compounds dictates that they are typically rich in heteroatoms, and therefore these methods of purification are often unsuccessful. Alternatively, residual metals can often be adsorbed onto activated charcoal<sup>6</sup> or functionalised solid supports.<sup>7–9</sup> In this case, additional filtration and washing sequences are required, and it is generally not possible to recover the catalyst.

The field of heterogeneous catalysis represents another practical alternative.<sup>10–15</sup> However, while much easier to separate following reaction, solid supported catalysts are typically associated with reduced rates of reaction, poorer selectivity, and potential catalyst leaching (leading to reduced catalyst loadings in subsequent reactions).<sup>16</sup>

Due to the propensity for weakly ligated gold(I) complexes to decompose in solution, an additional problem arises in oxidative gold catalysis when the external oxidant is fully consumed. It is known that gold(I) complexes readily disproportionate to form colloidal gold,<sup>17</sup> which cannot be easily recovered at the end of reaction, and may pose a risk of contamination to the reaction vessel. One possible solution to this problem would be to capture the gold catalyst as a stable complex, which can be easily isolated and recycled at the end of each reaction. If this isolated complex could also be used as a suitable pre-catalyst, then the active gold catalyst could simply be reintroduced to a fresh coupling reaction. Ideally, this would be facilitated by addition of an otherwise benign reagent (in catalytic quantities) able to promote the release of either a gold(I) or gold(III) species.



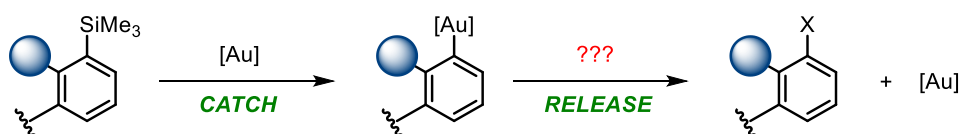
**Scheme 4.1.** The concept of ‘Catch and Release’ catalysis.

This sequence of ‘Catch and Release’ seeks to amalgamate the established benefits of homogeneous (reaction rate, selectivity) and heterogeneous (purification, recyclability) catalysis (Scheme 4.1).<sup>18</sup> In order to offer a viable alternative to current methods, the ‘catch’ step must be capable of removing the catalyst in an almost quantitative yield, such that the product is sufficiently purified of metal contaminants following treatment. Equally, the ‘release’ step must be as efficient as possible to avoid diminished catalyst loadings in the subsequent reaction(s).

Similar systems have been previously reported for other transition metal-catalysed reactions, typically involving separation by manipulating solubility in biphasic solutions,<sup>19–21</sup> or by taking advantage of reversible adsorption to a solid support.<sup>22–24</sup> Care must be taken to quantify the exact amount of catalyst that is activated and recovered in these systems, as the partial release of a highly active catalyst can create the illusion of complete recovery over a number of cycles.<sup>25</sup>

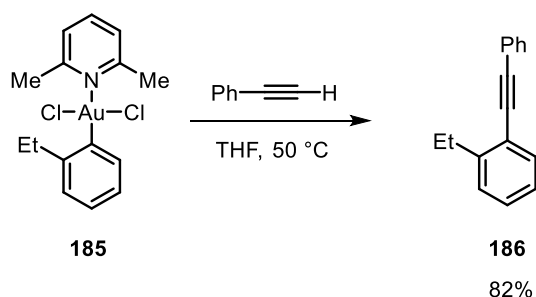
## 4.2. *Ortho*-Substituted Arylsilanes as Traps

The rapid rates of catalyst transmetalation, coupled with the unreactive nature of the resulting arylgold(III) species, highlighted the potential for *ortho*-substituted arylsilanes to be used as catalyst ‘traps’ in a Catch and Release protocol. While arylsilanes containing methyl, ethyl, and *iso*-propyl substituents at the 2-position (**113**, **132**, and **133**) had been found to slowly couple intermolecularly with 2-bromothiophene, larger *ortho*-substituents were shown to be completely unreactive under the original reaction conditions (see Chapter 2). Having already established the relative transmetalating ability of these substrates in the liquid phase, we sought to identify a method by which the catalyst could be released and reused (Scheme 4.2).



**Scheme 4.2.** Proposed “Catch and Release” sequence using *ortho*-substituted arylsilanes.

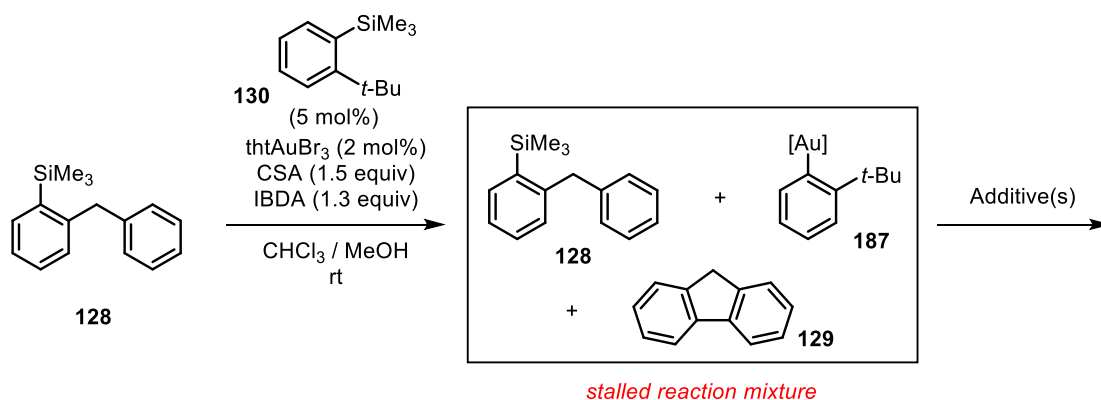
Fuchita and co-workers were able to demonstrate in stoichiometric studies that arylgold(III) species **185**, can undergo coupling with terminal alkynes to form diphenylacetylene products **186** (Scheme 4.3).<sup>26</sup> In contrast to the arylation reaction, in which an *ortho*-ethyl group severely reduces the rate of reaction, the alkynylation proceeds under fairly mild conditions (50 °C, 5 hours) to afford the coupled product in high yield. The linear geometry of the incoming alkyne nucleophile perhaps mitigates the steric hinderance to complexation, allowing coordination to occur despite the presence of an *ortho*-substituent. We therefore hypothesised that the addition of small, auraphillic nucleophiles may facilitate the coupling of the hindered gold(III) complexes and simultaneously allow the gold catalyst to be released.



**Scheme 4.3.** Fuchita’s stoichiometric alkynylation of arylgold(III) complex **185**.

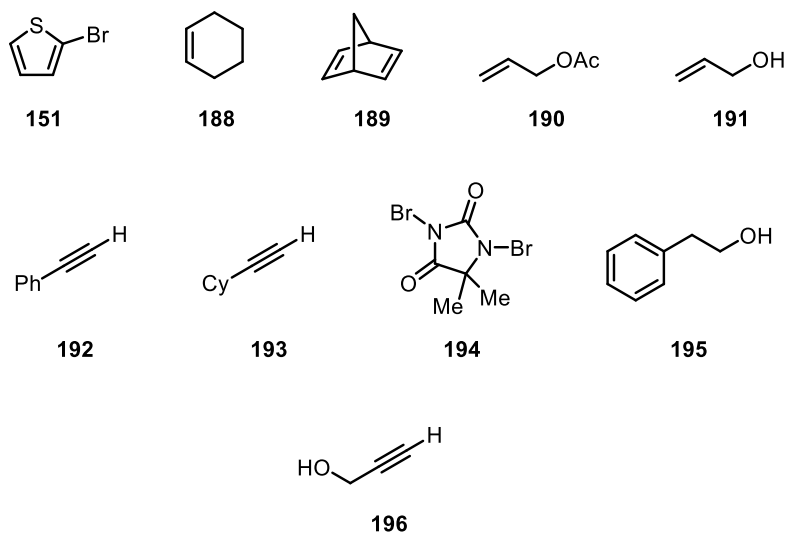
Ideally, any hypothetical release reaction would take place under the conditions required for arylation, and in the presence of the various reaction components. Therefore, to test the compatibility of various additives that may promote catalyst release, a trapping experiment

analogous to those in Chapter 2 was carried out, and different additives added to the stalled reaction after a given time. Should an additive successfully react to release the catalyst, then the reaction would simply restart, and formation of additional product would be detected (Scheme 4.4). Additives were selected based on perceived compatibility with the reaction conditions, and as a result the use of reductants or organometallic reagents was excluded due to the requirement for the oxidative and acidic components of the reaction.



**Scheme 4.4.** Trapping and attempted release promoted by the additives listed in Table 4.1 (below).

Additives:



**Figure 4.1.** Structures of additives used in the attempted release reaction.

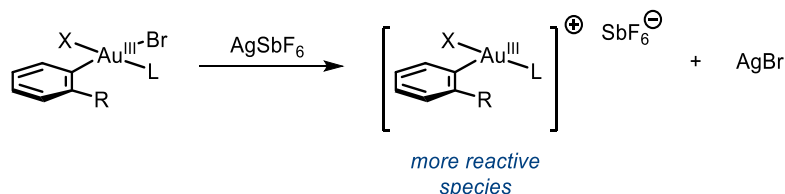
**Table 4.1.** Screening of additives in the attempted release of gold(III) from complex **187**.

Entry	Additive / Conditions	Comment	Entry	Additive / Conditions	Comment
<b>1</b>	-	a	<b>26</b>	<b>193</b> (0.5 eq)	b
<b>2</b>	Under sunlight	a	<b>27</b>	Entry 7 + <b>190</b> (0.5 eq)	b
<b>3</b>	In darkness	a	<b>28</b>	Entry 7 + <b>191</b> (0.5 eq)	b
<b>4</b>	<b>151</b> (0.5 eq)	b	<b>29</b>	Entry 7 + <b>192</b> (0.5 eq)	b
<b>5</b>	<b>151</b> (1.0 eq)	b	<b>30</b>	Entry 7 + <b>193</b> (0.5 eq)	b
<b>6</b>	<b>151</b> (5.0 eq)	b	<b>31</b>	TFA (1.0 eq)	b,c
<b>7</b>	AgSbF <sub>6</sub> (0.25 eq)	b	<b>32</b>	TFA (5.0 eq)	b,c
<b>8</b>	As above + <b>151</b> (1.0 eq)	b	<b>33</b>	NBS (0.25 eq)	b,d
<b>9</b>	AgPF <sub>6</sub> (0.25 eq)	b	<b>34</b>	NBS (0.5 eq)	b,d
<b>10</b>	As above + <b>151</b> (1.0 eq)	b	<b>35</b>	NBS (1.0 eq)	b,d
<b>11</b>	AgBF <sub>4</sub> (0.25 eq)	b	<b>36</b>	Selectfluor (0.25 eq)	b
<b>12</b>	As above + <b>151</b> (1.0 eq)	b	<b>37</b>	Selectfluor (0.5 eq)	b
<b>13</b>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (0.5 eq)	b	<b>38</b>	Selectfluor (1.0 eq)	b
<b>14</b>	CuI (0.5 eq)	b	<b>39</b>	HCl in Et <sub>2</sub> O (0.5 eq)	b,c
<b>15</b>	CuCl (1.0 eq)	b	<b>40</b>	HCl in Et <sub>2</sub> O (1.0 eq)	b,c
<b>16</b>	KF (0.25 eq)	b	<b>41</b>	HCl in Et <sub>2</sub> O (5.0 eq)	b,c
<b>17</b>	PPh <sub>3</sub> (1.0 eq)	b	<b>42</b>	<b>194</b> (0.25 eq)	b,d
<b>18</b>	DMSO (1.0 eq)	b	<b>43</b>	<b>194</b> (0.5 eq)	b,d
<b>19</b>	DMSO (5.0 eq)	b	<b>44</b>	BnOH (1.0 eq)	b
<b>20</b>	TFE (5.0 eq)	b	<b>45</b>	PhEtOH (1.0 eq)	b
<b>21</b>	<b>188</b> (0.5 eq)	b	<b>46</b>	<b>195</b> (0.5 eq)	b
<b>22</b>	<b>189</b> (0.5 eq)	b	<b>47</b>	Entry 7 + <b>196</b> (0.5 eq)	b
<b>23</b>	<b>190</b> (0.5 eq)	b			
<b>24</b>	<b>191</b> (0.5 eq)	b			
<b>25</b>	<b>192</b> (0.5 eq)	b			

[a] Reaction stalled at 23% conversion; [b] No additional product formed after addition of additive; [c] Protodesilylation observed; [d] Bromodesilylation observed.

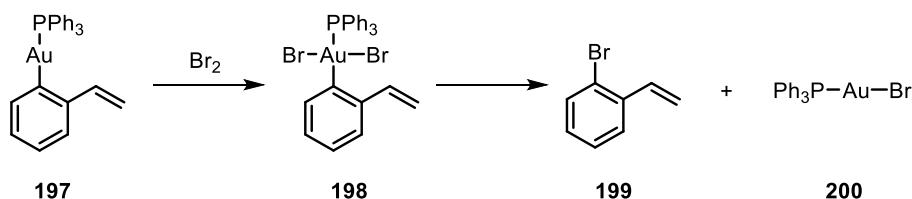
In the absence of any additive, other than the trap, the reaction reliably stalled at 23%, as confirmed by <sup>1</sup>H NMR spectroscopy. As expected based on the earlier trapping experiments, addition of an arene coupling partner (even in significant excess) failed to promote the release reaction (Entries 4 to 6). Silver salts are often used as additives in gold catalysis, proposed to

activate complexes *via* halide abstraction (Scheme 4.5).<sup>27–30</sup> In this case however, addition of a number of silver salts, either alone or in combination with 2-bromothiophene, failed to promote a successful release reaction (Entries 7 to 12).



**Scheme 4.5.** Proposed activation of the trapped gold(III) complex by silver-mediated halide abstraction.

A range of metal salts were tested in an attempt to promote C–X reductive elimination (X = OAc, F, Cl, I), but were typically insoluble and proved ineffective (Entries 13 to 16).<sup>31</sup> Vasapollo and co-workers reported that Gold(III) phosphine complex **198** was found to undergo C–Br reductive elimination to form bromostyrene **199** at room temperature (Scheme 4.6).<sup>32</sup> Addition of triphenylphosphine though failed to promote the analogous reaction in this instance (Entry 17).



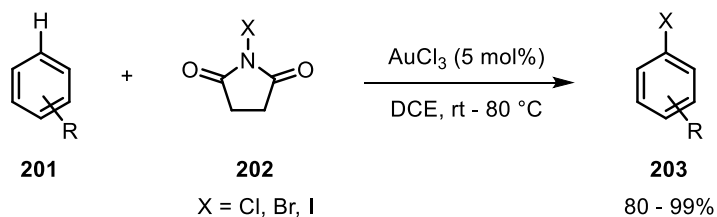
**Scheme 4.6.** Observation that complex **198** undergoes C–Br reductive elimination.

Addition of co-solvents that were known to accelerate the intermolecular arylation reaction did not facilitate the desired release reaction (Entries 18 to 20).<sup>33</sup> In addition to the alkynylation reported by Fuchita and co-workers (Scheme 4.6), a select number of alkene insertion reactions at gold(III) have been reported in the recent literature.<sup>34–37</sup> However, the addition of a variety of alkenes under these reaction conditions proved unsuccessful, and evidence of polymerisation was often detected (Entries 21 to 30). Incorporation of an alcohol to the additive, anticipated to aid coordination to the metal catalyst, had no noticeable effect (Entries 42 to 47).

Protodeauration, of alkyl,<sup>38</sup> alkenyl,<sup>39</sup> and aryl groups,<sup>38</sup> is a key step in many gold(I) catalysed reactions, though it is comparatively less common for gold(III) complexes.<sup>40</sup> Addition of acids to the arylation reaction mixture failed to promote release of the catalyst species, even in large

excess, and resulted in significant protodesilylation of the substrate (Entries 31, 32, and 39 to 41).

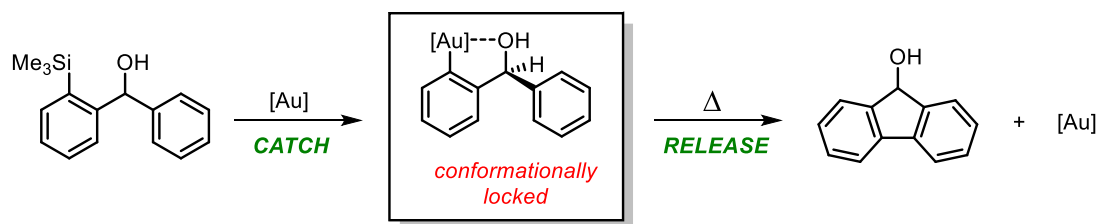
Wang and co-workers reported an electrophilic halogenation of arenes in the presence of a gold(III) catalyst using *N*-halosuccinimides (Scheme 4.7).<sup>41</sup> The mechanism is not clear however, and may involve Lewis Acid activation of the succinimide reagent rather than C-H auration. When electrophilic halogenating reagents were used in the attempted release reaction, halogenation of the trap could not be detected and bromodesilylation of the substrate was instead observed (Entries 33 to 38).



**Scheme 4.7.** Wang's electrophilic halogenation of simple aromatics in the presence of a gold(III) catalyst.

### 4.3. Restricted Rotation Traps

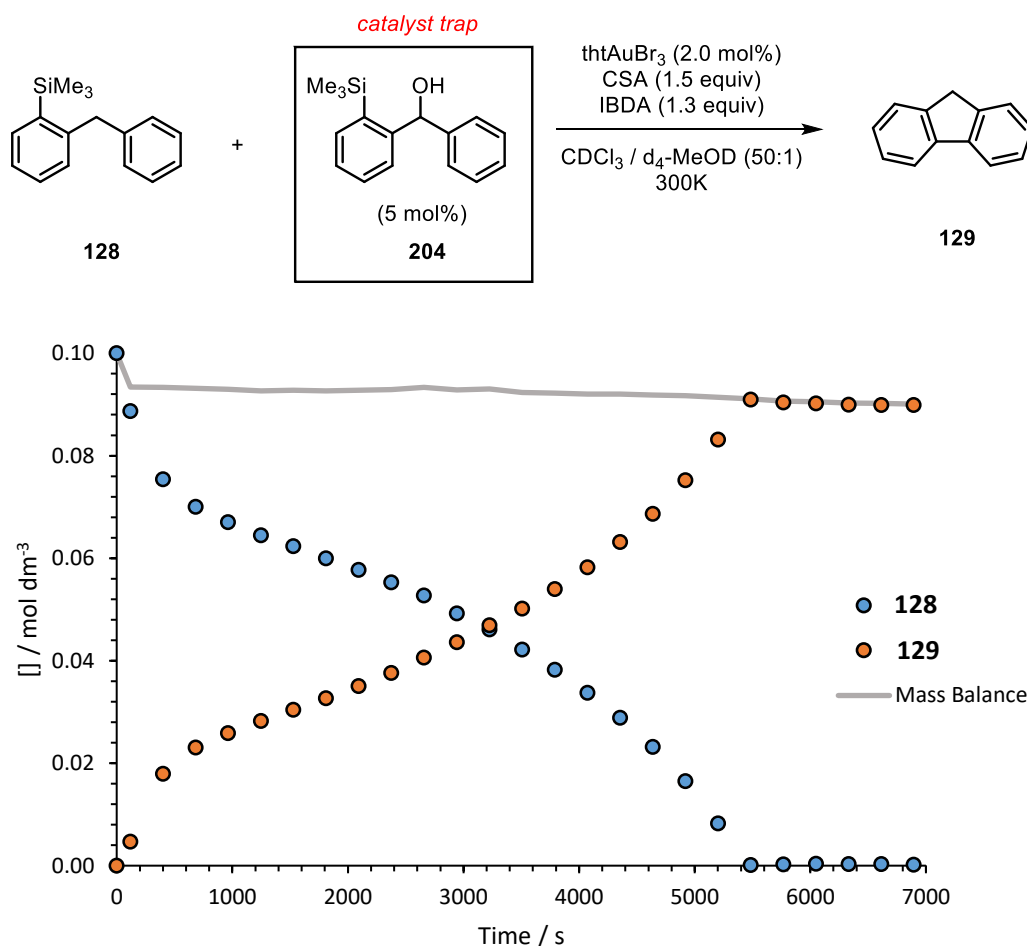
Inspired by the results in Chapter 3, in which tethered alcohols were found to effectively coordinate to the metal centre, we hypothesised that incorporation of an alcohol to the bridging methylene unit of cyclisation substrates might prevent the intramolecular arylation from taking place (Scheme 4.8). Strong binding through the alcohol would prevent  $\pi$ -complexation of the aryl group (on conformational grounds) and therefore prevent the cyclisation. Breaking the coordination (*e.g.*, by increasing the temperature) would then allow the required  $\pi$ -complexation to occur and the cyclisation would proceed with expulsion of the catalyst.



**Scheme 4.8.** Proposed mechanism of “Catch and Release” using restricted rotation.

The attempted use of arylsilane **204** as catalyst trap in the cyclisation reaction of **128** resulted in a significant reduction in the rate of reaction (ordinarily complete in <1000 seconds), but failed to completely stop the catalysis (Scheme 4.9).

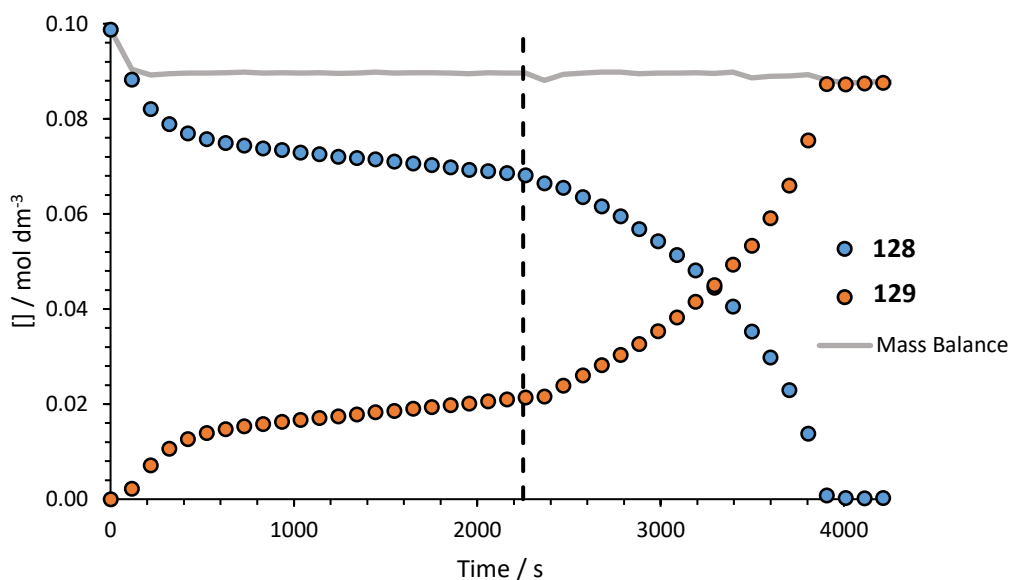




**Scheme 4.9.** Attempted trapping experiment with 5 mol% **204**.

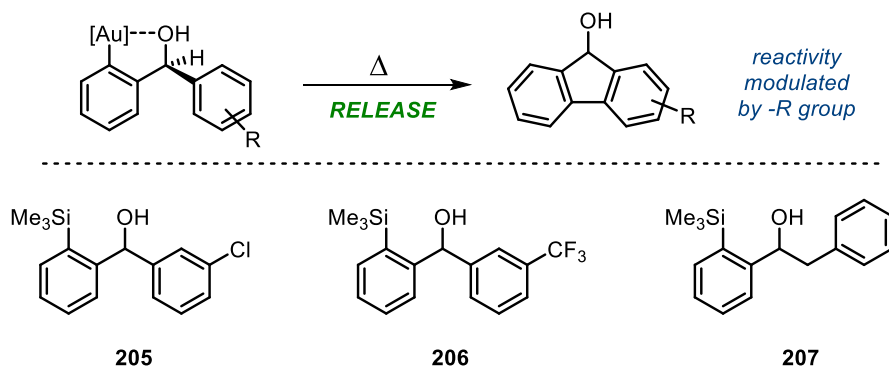
The sigmoidal appearance of the reaction profile can be rationalised as follows. Initial competition for the catalyst results in deceleration of the reaction rate, until the resting state of the catalyst has shifted from the (usual) pre-reductive elimination species to the ‘trapped’ complex. Slow cyclisation of the trap allows the catalyst to turnover and re-enter the cycle. This process repeats until all of the trap is fully consumed, resulting in a gradual acceleration in rate throughout the latter part of the reaction (as the concentration of available trap decreases).

The release process can be greatly accelerated by increasing the reaction temperature by 15 °C, demonstrating the potential for a thermally-triggered release (Figure 4.2).



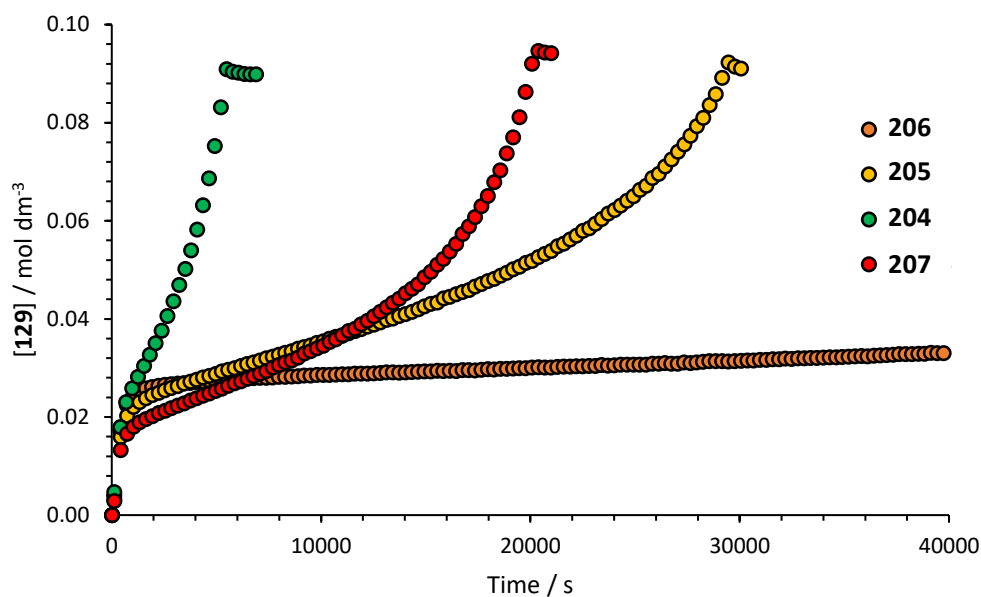
**Figure 4.2.** Trapping by **204** and attempted release by increasing temperature to 315 K.

However, in order to act as a viable trap in a Catch and Release protocol, the release reaction must be controlled such that it does not take place to any appreciable degree during the “Catch” step. We hypothesised that the reactivity of the trap in the catalyst-releasing cyclisation reaction could be modulated by either lengthening the linker between the arenes, or incorporating electron-withdrawing substituents on the tethered arene (Scheme 4.10).

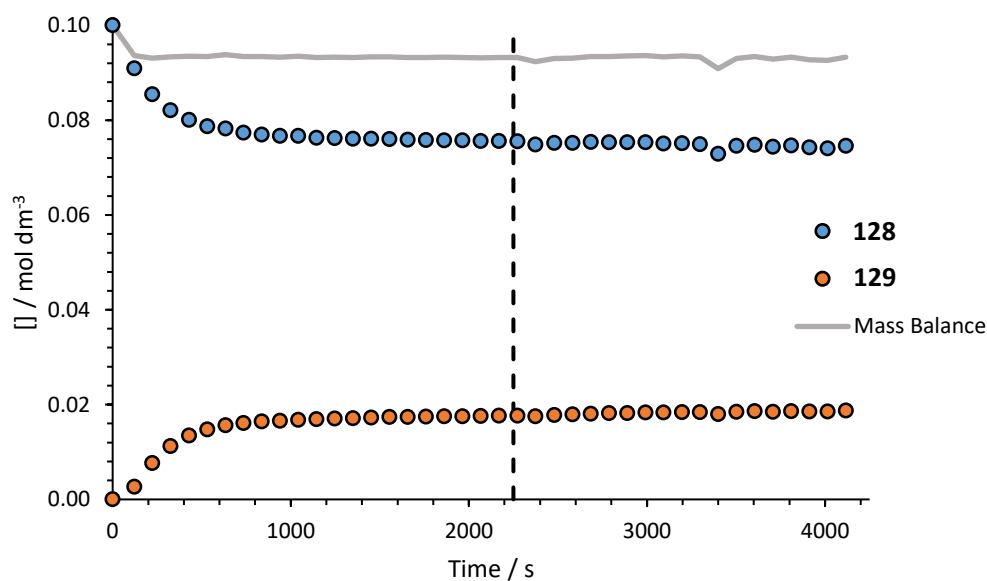


**Scheme 4.10.** Modification of catalyst trap in order to alter the rate of the release reaction.

This resulted in a similar rate of catalyst capture, but with the rate of catalyst release decreasing as a function of the electron-withdrawing capability of the substituent on the arene (Figure 4.3). The  $\text{-CF}_3$  substituent was sufficiently electron-withdrawing to entirely prevent the release reaction from taking place under the ambient reaction conditions. The lengthened tether of **207** led to a slightly accelerated rate of catalyst trapping, but did not prevent the cyclisation of the trap at room temperature.



**Figure 4.3.** Kinetic profile of catalyst trapping and release with compounds **204** to **207** at 300 K.



**Figure 4.4.** Trapping by **206** ( $\text{CF}_3$ ) at 300 K and attempted release by increasing temperature to 315 K.

Attempted thermal release however, proved unsuccessful using the same increase in temperature as previously (Figure 4.4). The temperature was not increased further owing to concern over the stability of the *in situ* formed oxidant, and therefore future efforts would likely require an alternative oxidant to be identified.

#### 4.4. Summary

The development of a suitable method for catalyst recovery is an important, but presently unsolved problem in oxidative gold catalysis. It is particularly pertinent in reactions such as direct arylation, which operate under nominally “ligand-free” conditions, as the stability of the related gold(I) species are generally poor. As discussed in the body of this chapter, the recovery of the catalyst is an issue that must be addressed if the reaction is to be amenable to large-scale industrial synthesis.

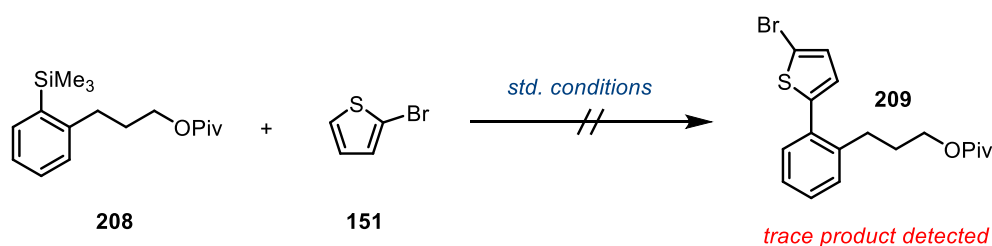
The rapid rates of transmetalation of *ortho*-substituted arylsilanes, coupled with the highly stable nature of the resulting gold(III) complexes, suggested that these reagents may be suitable catalyst “traps” for use in a Catch and Release protocol. While much was known about the kinetic behaviour of the “Catch” step (detailed in Chapter 2), the possibility of a “Release” reaction had not been investigated. Unfortunately, we have not yet been able to identify a suitable method through which to release the gold(III) species under catalytically relevant conditions. This can likely be attributed to the high kinetic stability of the trapped complex, in addition to compatibility issues between the various additives tested and the other reaction components.

An alternative method, involving intramolecular arylation substrates that had been modified to prevent cyclisation, was more promising. The reactivity of these traps in the “Release” reaction could be modulated by controlling the electronic properties of the tethered arene. A -CF<sub>3</sub> substituted trap was found to form a stable trapped complex at room temperature, offering the possibility of a thermally triggered release of the catalyst. In order to test the higher temperatures required to promote this reaction, an alternative, more thermally stable oxidant would be needed.

## 4.5. Future Work

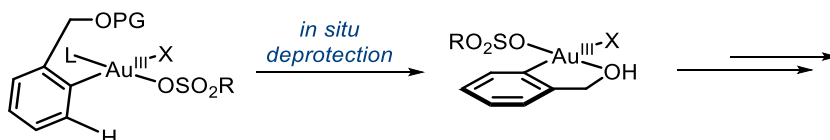
### 4.5.1. Protected Alcohols as Catalyst Traps

The contrasting reactivity of simple alkyl-substituted arylsilanes compared to those incorporating a tethered alcohol appealed as a potential opportunity for a catch and release manifold. Design of a chemical switch that allows trapping as an alkyl-substituted substrate, but coupling as a tethered alcohol, would provide the necessary control to trap and release the catalyst at will. While short-chain protected alcohols could undergo efficient arylation under typical reaction conditions, longer tethers were accompanied by a significant drop in reactivity. For example, pivalyl-protected alcohol **208** was effectively unreactive in the attempted coupling with 2-bromothiophene (Scheme 4.11).

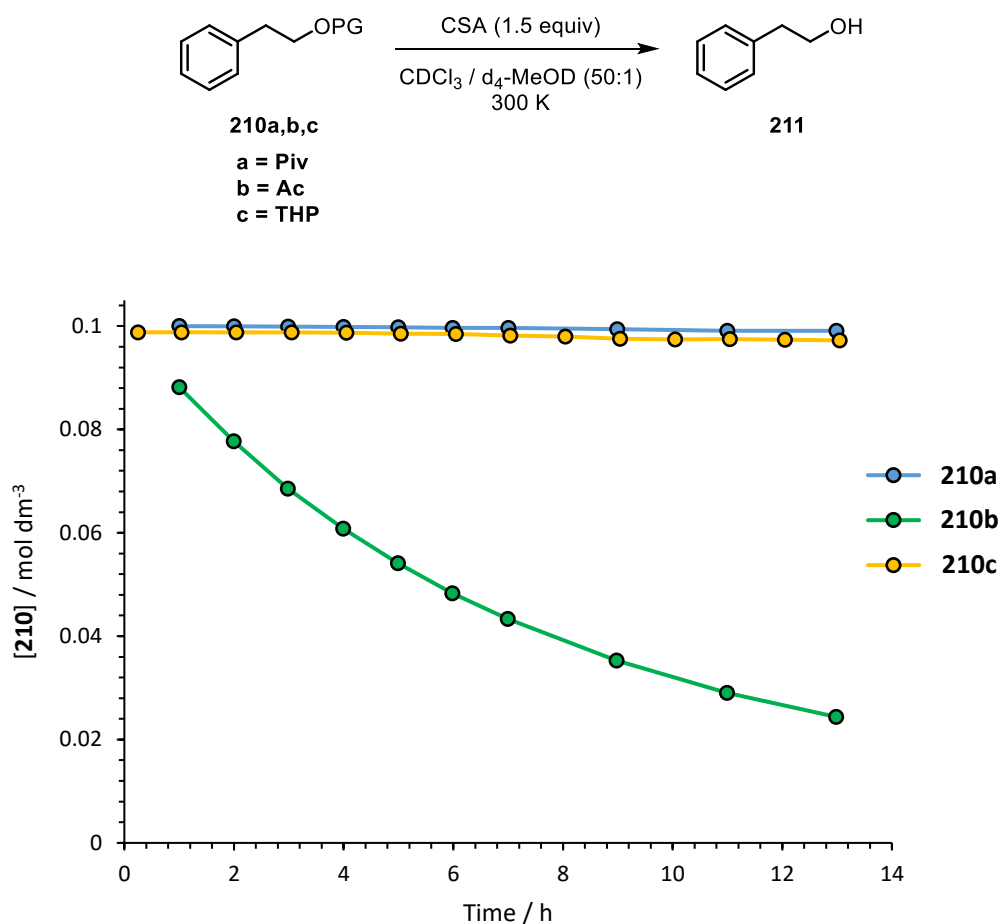


**Scheme 4.11.** Unsuccessful coupling of pivaloyl-protected alcohol **208** in arylation.

Identification of a protecting group that is tolerant of the reaction conditions, but can be selectively cleaved by addition of a suitable reagent, would allow facile interconversion between the trapped and reactive species (Scheme 4.12).



**Scheme 4.12.** Proposed strategy for a Catch and Release sequence using protecting groups.

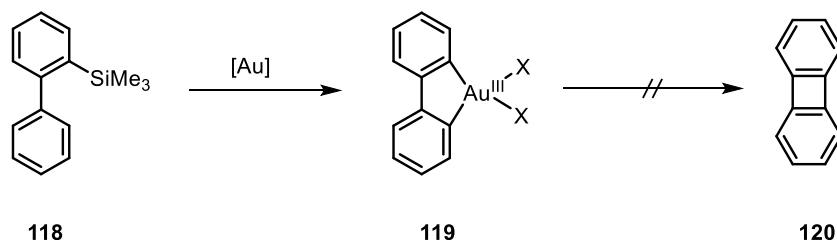


**Figure 4.13.** Stability of protecting groups under relevant acidic conditions.

While an acetate ester was slowly cleaved in the presence of CSA at room temperature, Piv- and THP-protected alcohols exhibited impressive stability, showcasing their potential as protecting groups to use in the Catch and Release sequence (Scheme 4.13). A successful release reaction would require the identification of a selective deprotection reaction to trigger controlled release of the free alcohol. To this end, photolabile protecting groups might offer a unique solution.<sup>42,43</sup>

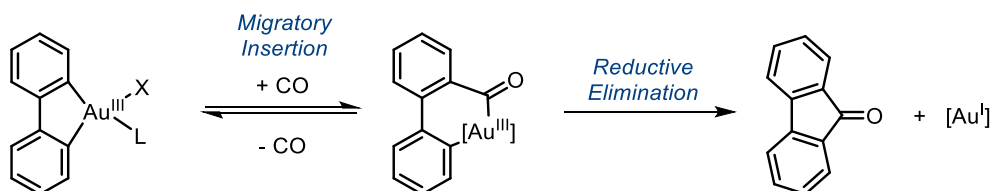
### 4.5.2. Metallocycle Expansion

As discussed in Chapter 2, (*o*-biphenyl)trimethylsilane **118** is known to undergo reaction with the active gold catalyst used in arylation to form the stable metallocycle **119** (Scheme 4.14).<sup>44</sup> The reductive elimination to form biphenylene, **120**, does not occur at room temperature,<sup>xx</sup> presumably due to the high energetic barrier associated with the introduction of such significant bond strain.<sup>45</sup> As a result, the metallocycle is a stable, long-lived species, and has even been demonstrated to be a competent Lewis Acid catalyst for a multitude of transformations.<sup>46</sup>



**Scheme 4.14.** Formation of stable metallocycle XX via sequential C-Si and C-H auration.

While classical migratory insertion reactions at gold(III) are uncommon, this elementary step is currently the focus of much attention in the field.<sup>34</sup> Development of a suitable insertion reaction in this case would result in a metallocycle ring expansion (Scheme 4.15). The energetic barrier to reductive elimination could be expected to be significantly lowered, perhaps allowing cyclisation to occur.



**Scheme 4.15.** Release reaction enabled by a hypothetical (CO) migratory insertion.

This sequence could allow a catch and release method to be developed, relying on the straightforward introduction of a gaseous reagent (*e.g.*, carbon monoxide) to promote the release of an active gold species.

<sup>xx</sup> The (reverse) oxidative addition into the C-C bond of biphenylene has been demonstrated to be possible using a gold(I) pre-cursor.<sup>46,47</sup>

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**Experimental**

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## 5.1 General Experimental Details

### 5.1.1 Techniques

Procedures that involve the use of air- and/or moisture-sensitive reagents were performed in anhydrous solvents, using standard inert-atmosphere techniques under an atmosphere of N<sub>2</sub> (unless otherwise stated). Where necessary, solvents were degassed following a freeze-pump-thaw sequence for a minimum of 3 cycles. Room temperature (rt) typically fluctuated between 18 – 25 °C depending on the season and time of day. Reaction temperatures were controlled using a Heidolph MR Hei-Standard stirrer hotplate equipped with Teflon coated thermocouple.

### 5.1.2 Reagents and Solvents

Reaction solvents tetrahydrofuran (THF) (unstabilised, HPLC grade; Sigma-Aldrich), diethyl ether (Et<sub>2</sub>O) (EtOH stabilised, HPLC grade; VWR), toluene (HPLC grade; Fisher), and dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) (unstabilised, HPLC grade; Fisher) were dried by percolation through columns packed with neutral alumina under a positive pressure of argon. Reaction solvents chloroform (CHCl<sub>3</sub>) (amylene stabilised, HPLC grade; Sigma-Aldrich) and chloroform-d (CDCl<sub>3</sub>) (99.8 atom % D; Sigma-Aldrich) were passed through a short plug of basic activated alumina (Al<sub>2</sub>O<sub>3</sub>; Brockman I) and held over 3 Å molecular sieves under N<sub>2</sub>, in the dark and used within one month. Trimethylsilyl chloride was distilled over calcium hydride (CaH<sub>2</sub>) prior to use and stored under an atmosphere of N<sub>2</sub> at 0 °C. Other silyl chlorides were purchased and used as received unless otherwise stated. Gold(III) bromide (99%, 99.9% Au) was purchased from STREM chemicals and used as received. Unless otherwise stated, reagents were purchased from Sigma-Aldrich, Fluorochem, VWR, Apollo Scientific, Fisher Scientific, or Alpha Aesar, and used without additional purification.

### 5.1.3 Chromatography

Analytical thin-layer chromatography was performed on pre-coated aluminum-backed plates (Silica Gel 60 F254; Merck) or pre-coated glass-backed plates (Silica Gel 60 F254; Merck), and visualised under ultraviolet (UV) light (254 nm). Where appropriate, plates were treated with aqueous basic potassium permanganate, ethanolic phosphomolybdic acid, or vanillin stains. Preparative thin-layer chromatography (PTLC) was performed on pre-coated, analytical aluminium-backed plates (Silica Gel 60 F254; Merck) or glass-backed plates (Silica

Gel 60 F254; Merck). Flash column chromatography was performed using Geduran® Silica Gel 60 (40-63  $\mu\text{m}$ ; Merck).

#### **5.1.4 Analysis**

##### **5.1.4.1 NMR Spectroscopy**

All NMR spectra were acquired using a Bruker Avance III+ 400 MHz spectrometer.  $^1\text{H}$ ,  $^{13}\text{C}\{^1\text{H}\}$ ,  $^{19}\text{F}$ , and  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra were acquired at 400, 100, 376, and 162 MHz respectively. Unless otherwise stated, NMR spectra were acquired at 300 K (27 °C).  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra were referenced to residual and bulk solvent signals respectively; chemical shifts are reported in parts per million (ppm) relative to residual chloroform ( $\text{CHCl}_3$ ,  $\delta_{\text{H}}$  7.26 ppm;  $\text{CDCl}_3$ ,  $\delta_{\text{C}}$  77.16 ppm) or methanol ( $\text{CH}_3\text{OH}$ ,  $\delta_{\text{H}}$  3.31 ppm;  $\text{CD}_3\text{OD}$ ,  $\delta_{\text{C}}$  49.00 ppm).  $^{19}\text{F}$  and  $^{31}\text{P}$  NMR spectra are reported in ppm relative to external standards. Coupling constants ( $J$ ) were calculated using MestreNova v9.0 software and are reported to the nearest 0.1 Hz. The following abbreviations (and their combinations) are used to denote signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), app (apparent) and br (broad). Quantitative  $^{19}\text{F}$  NMR were recorded using 1,3,5-trifluorobenzene as an internal standard ( $\delta_{\text{F}}$  -107.48 ppm in  $\text{CDCl}_3$ ).

##### **5.1.4.2 IR Spectroscopy**

Infrared (IR) absorption spectra of neat compounds were recorded over the range 4000 – 400  $\text{cm}^{-1}$  using a Bruker Alpha FT-IR spectrometer equipped with a Bruker Platinum Quicksnap (diamond cell) attachment. Peaks are reported in  $\text{cm}^{-1}$  with relative intensities denoted by the following abbreviations (and their combinations): s (strong, 0–33% T), m (medium, 34–66% T), w (weak, 67–100% T), and br (broad).

##### **5.1.4.3 Mass Spectrometry**

Mass spectra were recorded on either ThermoElectron MAT 900 or Bruker ESI Micro-Tof spectrometers.

#### **5.1.4.4    *Melting Points***

Melting points (mp) were determined using a Griffin capillary melting point apparatus using open 100 mm soda glass capillary tubes and are reported uncorrected.

#### **5.1.5    Kinetic Modelling and Simulations**

The fitting and simulation of reaction kinetics was carried out using DynoChem resources software.

## 5.2 Reaction Monitoring

### 5.2.1 Standard *in situ* NMR Reaction Monitoring Procedure

The requisite arylsilane (0.10 mmol) was weighed into a 7 mL screw-capped vial.  $\text{CDCl}_3$  (1 mL),  $\text{MeOD-d}_4$  (20  $\mu\text{L}$ ),  $\text{thtAuBr}_3$  (0.002 mmol, 2 mol%, from a 0.01 M stock solution), and the requisite arene (0.10 mmol) were added and the resulting solution transferred to a standard borosilicate NMR tube. The sample was injected into the spectrometer; locked, shimmed, and tuned, before a ( $t = 0$ ) spectrum was acquired. Once the appearance of this initial spectrum was deemed suitable the sample was ejected from the spectrometer and the contents of the tube poured into a 7 mL screw-capped vial containing HCIB (58.8 mg, 0.13 mmol). The mixture was shaken until visibly homogenous (typically < 5 seconds) then returned to the NMR tube, and again injected into the spectrometer. Spectra were acquired at regular intervals as required depending on the rate of reaction.

For  $^1\text{H}$  NMR experiments,  $\text{CH}_2\text{Br}_2$  was typically employed as an internal standard. In some cases (as specified) a mixture of IBDA (41.9 mg, 0.13 mmol) and CSA (34.8 mg, 0.15 mmol) was used in place of HCIB.

*Note: The time of the first data point was measured (by stopwatch) from the point of mixing to the midpoint of the first NMR experiment.*

### 5.2.2 Standard Reaction Monitoring Procedure

The requisite arylsilane (0.10 mmol) was weighed into a 7 mL screw-capped vial.  $\text{CDCl}_3$  (1 mL),  $\text{MeOD-d}_4$  (20  $\mu\text{L}$ ),  $\text{thtAuBr}_3$  (0.002 mmol, 2 mol%, from a 0.01 M stock solution), and the requisite arene (0.10 mmol) were added and the resulting solution transferred to a standard borosilicate NMR tube. The sample was injected into the spectrometer and a spectrum acquired using the automation interface. The sample was ejected from the spectrometer and the contents of the tube poured into a 7 mL screw-capped vial containing HCIB (58.8 mg, 0.13 mmol). The mixture was shaken until visibly homogenous (typically < 5 seconds) then returned to the NMR tube, and spectra acquired at regular intervals. The sample was ejected from the spectrometer between experiments, allowing for multiple reactions to be performed in parallel. The spectrometer was housed in a room in which the ambient temperature, and therefore reaction temperature, was controlled (at 294 K).

*Note: The time of the first data point was measured (by stopwatch) from the point of mixing to the midpoint of the first NMR experiment.*

### 5.2.3 Sample Preparation for Trapping Experiments

A 500  $\mu\text{L}$  aliquot of Stock Solution A; containing the arylsilane substrate (0.10 mmol),  $\text{MeOD-d}_4$  (20  $\mu\text{L}$ ),  $\text{CH}_2\text{Br}_2$  (0.10 mmol), and  $\text{tHtAuBr}_3$  (0.002 mmol, 2 mol%) in  $\text{CDCl}_3$ , was transferred to a 7 mL screw-capped vial. The arylsilane trap (X mol%) was added, by weight, from a 0.025 M stock solution in  $\text{CDCl}_3$  (Stock Solution B). The reaction volume was made up to 1 mL with additional  $\text{CDCl}_3$ , added *via* syringe. This sample was then analysed according to the Standard *in situ* Reaction Monitoring Procedure.

Stock solutions were prepared fresh and used within 12 hours to avoid ingress of moisture.

*Note: The exact concentration of arylsilane trap was calculated based on the mass of stock solution added.*

## 5.3 General Procedures

### 5.3.1 Procedure A

The requisite arylsilane (1.00 mmol) was weighed into a 30 mL screw-capped vial equipped with magnetic stirrer bar.  $\text{CHCl}_3$  (10 mL), MeOH (0.2 mL),  $\text{tHtAuBr}_3$  (10.5 mg, 0.02 mmol, 2 mol%), and the requisite arene (1.00 mmol) were added and stirring commenced. HCIB (588 mg, 1.30 mmol) was added in one portion, a screw cap fitted, and the reaction stirred at room temperature for the length of time indicated. The crude reaction mixture was then dry-loaded on to silica and purified by column chromatography as described in each case.

### 5.3.2 Procedure B

The requisite arylsilane (0.50 mmol) was weighed into a 30 mL screw-capped vial equipped with magnetic stirrer bar.  $\text{CHCl}_3$  (5 mL), MeOH (0.1 mL),  $\text{tHtAuBr}_3$  (5.3 mg, 0.01 mmol, 2 mol%), and the requisite arene (0.50 mmol) were added and stirring commenced. HCIB (294 mg, 0.65 mmol) was added in one portion, a screw cap fitted, and the reaction stirred at room temperature for the length of time indicated. The crude reaction mixture was then dry-loaded on to silica and purified by column chromatography as described in each case.

### 5.3.3 Procedure C

The requisite arylsilane (0.10 mmol) was weighed into a 7 mL screw-capped vial equipped with magnetic stirrer bar.  $\text{CHCl}_3$  (1 mL), MeOH (20  $\mu\text{L}$ ),  $\text{tHtAuBr}_3$  (0.002 mmol, 2 mol%, from a stock solution), and the requisite arene (0.10 mmol) were added and stirring commenced. HCIB (58.8 mg, 0.13 mmol) was added in one portion, a screw cap fitted, and the reaction stirred at room temperature for 72 hours. The volatiles were removed under reduced pressure, and the residue purified by preparative TLC using the elution solvent indicated in each case.



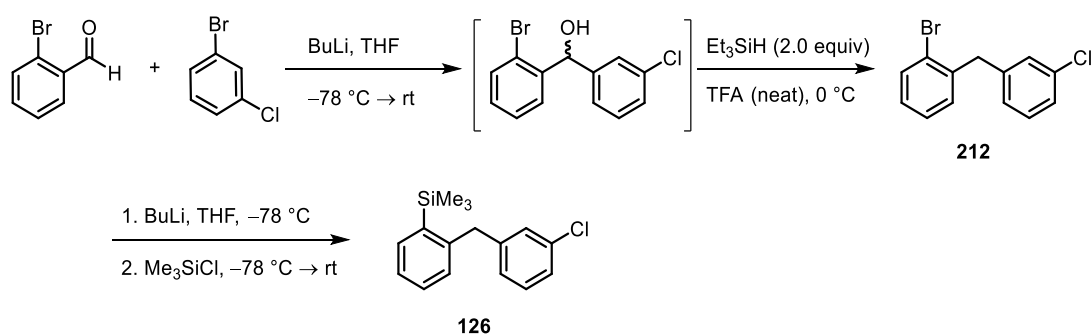
## 5.4 Synthetic Procedures

thtAuBr<sub>3</sub>,<sup>1</sup> 1-*tert*-butyl-2-iodobenzene,<sup>2</sup> HPDMS-Cl,<sup>1</sup> and HCIB,<sup>3</sup> were synthesised according to literature procedures.

(2-Methylphenyl)trimethylsilane (**113**) and 2-(trimethylsilyl)phenol were prepared and characterised by Dr Liam Ball as previously reported.<sup>4,5</sup>

### 5.4.1 Arylsilanes

#### 5.4.1.1 Preparation of Cyclisation Substrates 126 and 128



#### 1-Bromo-2-(3-chlorobenzyl)benzene (**212**)

To a nitrogen filled, flame-dried Schlenk flask was added 1-bromo-3-chlorobenzene (3.26 g, 17.0 mmol) along with dry THF (40 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (2.38 M in hexanes, 8.00 mL, 19.0 mmol) was added dropwise over 15 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 60 mins, then 2-bromobenzaldehyde (2.50 mL, 21.5 mmol) was added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (25 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O (3  $\times$  30 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure to afford a highly viscous, pale yellow oil (crude mass = 3.74 g). Triethylsilane (4.0 mL, 25.0 mmol) was added dropwise, then the mixture was cooled to  $0\text{ }^{\circ}\text{C}$  and trifluoroacetic acid (15 mL) was added dropwise. The resulting solution was stirred at this temperature for 1 hour, then stirred at room temperature overnight. The remaining trifluoroacetic acid was removed under a rapid stream of nitrogen, and the resulting oil purified by column chromatography (eluent: hexanes) to afford the title compound as a pale yellow oil (3.03 g, 63%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.31 – 7.04 (m, 7H), 4.10 (s, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 141.5, 139.5, 134.3, 133.0, 131.1, 129.7, 129.0, 128.2, 127.6, 127.2, 126.5, 124.9, 41.4.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2919 (w), 2817 (w), 1595 (w), 1573 (w), 1557 (w), 1539 (w), 1505 (w), 1471 (m), 1429 (w), 1379 (w), 1190 (w), 1091 (w), 1078 (w), 1046 (w), 1024 (w), 976 (w), 932 (w), 876 (w), 797 (w), 774 (m), 751 (m), 728 (w), 682 (w), 659 (w), 435 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>6</sup>

### **[2-(3-Chlorobenzyl)phenyl]trimethylsilane (126)**

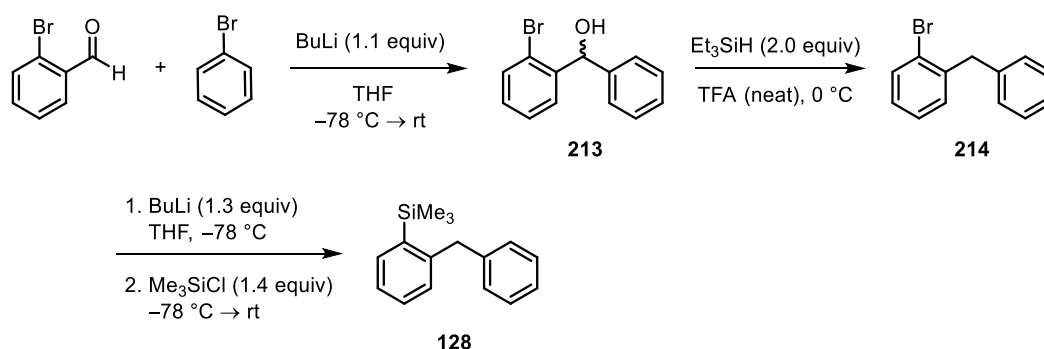
To a nitrogen filled, flame-dried Schlenk flask was added 1-bromo-2-(3-chlorobenzyl)benzene (3.03 g, 10.75 mmol) along with dry THF (25 mL). The solution was cooled to –78 °C and *n*-butyllithium (2.38 M in hexanes, 5.75 mL, 11.95 mmol) was added dropwise over 15 minutes. The mixture was stirred at –78 °C for a further 60 mins, then trimethylsilylchloride (2.00 mL, 15.75 mmol) was added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (30 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (2.03 g, 69%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.35 – 7.18 (m, 4H), 7.12 – 7.09 (m, 1H), 7.04 – 6.96 (m, 2H), 4.16 (s, 2H), 0.33 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 145.3, 143.7, 139.1, 134.8, 134.4, 130.0, 129.7, 129.6, 129.3, 127.4, 126.4, 125.9, 41.4, 0.5.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2953 (w), 2896 (w), 1596 (w), 1573 (w), 1474 (w), 1429 (w), 1262 (w), 1249 (m), 1186 (w), 1122 (w), 1092 (w), 1077 (w), 834 (s), 774 (m), 754 (m), 728 (m), 685 (m), 622 (w), 565 (w), 437 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>6</sup>



### (2-Bromophenyl)(phenyl)methanol (213)

To an N<sub>2</sub>-purged, flame-dried 250 mL RBF was added bromobenzene (3.37 mL, 32.0 mmol) along with dry THF (80 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (2.15 M in hexanes, 16.30 mL, 35.0 mmol) was added dropwise over 30 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 30 mins, then 2-bromobenzaldehyde (4.70 mL, 40.0 mmol) was added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (40 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O (3  $\times$  40 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a highly viscous, pale yellow oil (5.45 g, 65%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.59 (dd,  $J$  = 7.8, 1.8 Hz, 1H), 7.54 (dd,  $J$  = 8.0, 1.2 Hz, 1H), 7.43 – 7.25 (m, 6H), 7.15 (ddd,  $J$  = 8.0, 7.4, 1.7 Hz, 1H), 6.20 (d,  $J$  = 3.8 Hz, 1H), 2.39 (d,  $J$  = 3.9 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  142.7, 142.3, 133.0, 129.3, 128.6, 128.6, 127.9, 127.9, 127.2, 123.0, 74.9.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 3335 (br w), 1493 (w), 1465 (w), 1455 (w), 1436 (w), 1396 (w), 1182 (w), 1012 (m), 748 (m), 719 (w), 697 (m), 681 (w), 643 (w), 619 (w), 600 (w), 562 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>6</sup>

### 1-Benzyl-2-bromobenzene (214)

Triethylsilane (4.48 mL, 28.0 mmol) was added dropwise to a 250 mL RBF containing (2-bromophenyl)(phenyl)methanol (3.70 g, 14.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The mixture was cooled to 0  $^{\circ}\text{C}$  and trifluoroacetic acid (4.3 mL) was added dropwise. The resulting solution

was stirred at this temperature for 3 hours, then allowed to return to room temperature. The trifluoroacetic acid was removed under a rapid stream of nitrogen, and the resulting oil purified by column chromatography (eluent: hexanes) to afford the title compound as a pale yellow oil (3.30 g, 95%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.34 – 7.06 (m, 8H), 4.13 (s, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 140.5, 139.6, 133.0, 131.2, 129.1, 128.6, 128.6, 128.0, 127.6, 126.4, 125.1, 41.9.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 1494 (w), 1473 (w), 1464 (w), 1453 (w), 1437 (m), 1073 (w), 1045 (w), 1024 (m), 743 (m), 717 (m), 695 (m), 659 (w), 610 (w), 562 (w), 459 (w), 437 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>6</sup>

### [2-Benzylphenyl]trimethylsilane (128)

To a nitrogen filled, flame-dried Schlenk flask was added 1-bromo-2-(benzyl)benzene (3.30 g, 13.35 mmol) along with dry THF (35 mL). The solution was cooled to –78 °C and *n*-butyllithium (2.15 M in hexanes, 8.37 mL, 18.0 mmol) was added dropwise over 15 minutes. The mixture was stirred at –78 °C for a further 60 mins, then trimethylsilylchloride (2.54 mL, 20.0 mmol) was added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (20 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a colourless oil (3.05 g, 95%).

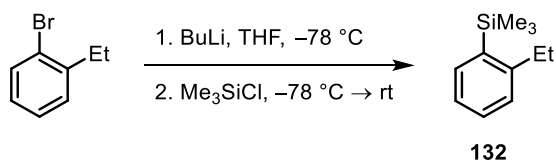
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.58 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.27 – 7.20 (m, 2H), 7.16 – 7.11 (m, 2H), 7.06 – 7.02 (m, 1H), 4.20 (s, 2H), 0.35 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 146.4, 141.6, 139.0, 134.7, 130.0, 129.5, 129.3, 128.5, 126.1, 125.6, 41.8, 0.5.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3058 (w), 3026 (w), 2952 (w), 2897 (w), 1587 (w), 1494 (w), 1465 (w), 1452 (w), 1435 (w), 1248 (m), 1122 (w), 1073 (w), 1030 (w), 833 (s), 743 (m), 725 (m), 696 (m), 622 (w), 563 (w), 439 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>6</sup>

#### 5.4.1.2 Preparation of *ortho*-Alkyl Substituted Arylsilanes



##### (2-Ethylphenyl)trimethylsilane (132)

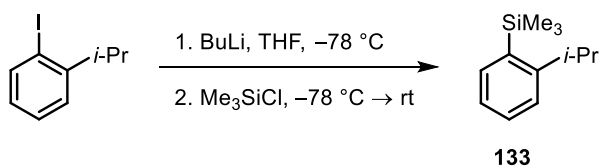
To a nitrogen filled, flame-dried Schlenk flask was added 1-bromo-2-ethylbenzene (1.87 mL, 13.5 mmol) followed by dry THF (30 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (2.15 M in hexanes, 7.0 mL, 15.0 mmol) was added dropwise over 15 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 60 mins, then trimethylsilylchloride (2.54 mL, 20.0 mmol) added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight (approximately 14 hours). Water (15 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (2.28 g, 95%).

**$^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.48 (dd,  $J = 7.4, 1.3\text{ Hz}$ , 1H), 7.34 (app. td,  $J = 7.5, 1.5\text{ Hz}$ , 1H), 7.24 (m, 1H), 7.18 (app. td,  $J = 7.5, 1.3\text{ Hz}$ , 1H), 2.79 (q,  $J = 7.5\text{ Hz}$ , 2H), 1.27 (t,  $J = 7.5\text{ Hz}$ , 3H), 0.35 (s, 9H).

**$^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  150.2, 138.0, 134.6, 129.5, 128.1, 125.1, 29.2, 16.6, 0.6.

**$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ :** 2962 (w), 2897 (w), 2873 (w), 1470 (w), 1453 (w), 1430 (w), 1248 (m), 1128 (w), 1084 (w), 1061 (w), 833 (s), 794 (m), 751 (m), 726 (w), 687 (w), 673 (w), 621 (w), 569 (w), 456 (w), 420 (w).

$^1\text{H}$  and  $^{13}\text{C}$  NMR data are consistent with those reported in the literature.<sup>7</sup>



**(2-*iso*-Propylphenyl)trimethylsilane (133)**

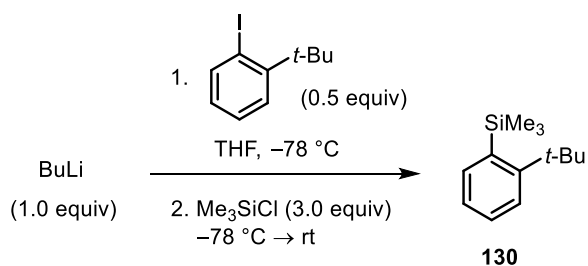
To a nitrogen filled, flame-dried Schlenk flask was added 1-iodo-2-*isopropyl*benzene (0.81 mL, 5.0 mmol) followed by dry THF (10 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (1.52 M in hexanes, 6.58 mL, 10.0 mmol) was added dropwise over 15 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 30 mins, then trimethylsilylchloride (1.91 mL, 15.0 mmol) added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (10 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O ( $3 \times 20\text{ mL}$ ). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (0.39 g, 41%).

**<sup>1</sup>H (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.46 (dd,  $J = 7.3, 1.4\text{ Hz}$ , 1H), 7.38 – 7.30 (m, 2H), 7.20 – 7.15 (m, 1H), 3.17 (hept,  $J = 6.7\text{ Hz}$ , 1H), 1.27 (d,  $J = 6.9\text{ Hz}$ , 6H), 0.34 (s, 9H).

**<sup>13</sup>C (100 MHz, CDCl<sub>3</sub>):**  $\delta$  155.2, 137.4, 134.4, 129.7, 125.3, 125.3, 33.9, 24.8, 0.6.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 2959 (w), 2868 (w), 1473 (w), 1458 (w), 1430 (w), 1248 (m), 1116 (w), 1068 (w), 834 (s), 761 (m), 728 (m), 687 (w), 676 (w), 621 (w), 547 (w), 460 (w).

**HRMS** Calcd. for C<sub>12</sub>H<sub>20</sub>Si: 192.1329 [M]<sup>+</sup>; found (EI<sup>+</sup>): 192.1321



### (2-*tert*-Butylphenyl)trimethylsilane (130)

*n*-Butyllithium (2.15 M in hexanes, 2.33 mL, 5.0 mmol) was added to a flame-dried Schlenk flask which had been evacuated and backfilled with nitrogen 4 times. The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and diluted with dry THF (3.0 mL). In a separate flame-dried flask, 2-*tert*-butyliodobenzene (0.65 g, 2.5 mmol) was dissolved in dry THF (2.5 mL) and then transferred dropwise by cannula to the solution of BuLi over approximately 20 minutes. Additional THF (approx. 1 mL) was used to transfer any residual iodoarene. The solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 45 mins and then trimethylsilylchloride (1.90 mL, 15.0 mmol) was added in one portion. The mixture was allowed to return to room temperature overnight (approx. 14 hours) and then quenched by cautious addition of  $\text{H}_2\text{O}$  (10 mL). Additional  $\text{Et}_2\text{O}$  (10 mL) was added and the two phases separated before the aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 15\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated in vacuo. The crude oil was purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (215 mg, 42%).

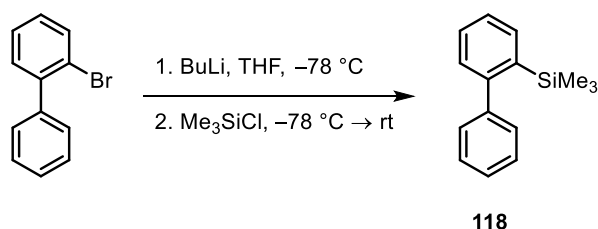
*Note: Attempts to synthesise the compound by addition of BuLi to the iodoarene resulted in consistent formation of material contaminated with 1-butyl-2-tert-butylbenzene which was inseparable from the desired compound by chromatography and fractional distillation.*

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.74 (dd,  $J = 7.5, 1.6\text{ Hz}$ , 1H), 7.49 (dd,  $J = 8.0, 1.3\text{ Hz}$ , 1H), 7.35 – 7.28 (m, 1H), 7.20 (app. td,  $J = 7.4, 1.3\text{ Hz}$ ), 1.44 (s, 9H), 0.45 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  156.8, 137.9, 137.1, 128.7, 125.6, 124.9, 37.0, 33.0, 4.2.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 3287 (br, w), 2952 (w), 2895 (w), 1434 (w), 1407 (w), 1247 (m), 1200 (w), 1125 (w), 1078 (w), 1010 (w), 834 (s), 743 (m), 728 (m), 687 (m), 622 (m), 604 (w), 460 (w), 429 (w).

**HRMS** Calcd. for  $\text{C}_{13}\text{H}_{22}\text{Si}$ : 206.1485  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 206.1492.



**(2-Biphenyl)trimethylsilane (118)**

To a nitrogen filled, flame-dried Schlenk flask was added 2-bromobiphenyl (1.0 mL, 5.80 mmol) along with dry THF (15 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (2.38 M in hexanes, 2.75 mL, 6.50 mmol) was added dropwise over 15 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 60 mins, then trimethylsilylchloride (0.90 mL, 7.00 mmol) added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (15 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with  $\text{Et}_2\text{O}$  ( $3 \times 20\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (0.98 g, 75%).

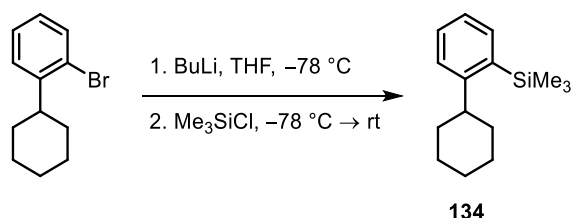
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.77 (m, 1H), 7.56 – 7.35 (m, 8H), 0.16 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  149.4, 144.6, 138.6, 134.8, 129.6, 129.5, 128.6, 127.8, 127.2, 126.4, 0.7.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2952 (w), 1557 (w), 1540 (w), 1507 (w), 1463 (w), 1442 (w), 1425 (w), 1247 (m), 1122 (w), 1087 (w), 1072 (w), 1008 (w), 834 (s), 750 (m), 728 (m), 701 (m), 622 (w), 553 (w), 459(w).

$^1\text{H}$  and  $^{13}\text{C}$  NMR data are consistent with those reported in the literature.<sup>5</sup>





**(2-Cyclohexylphenyl)trimethylsilane (134)**

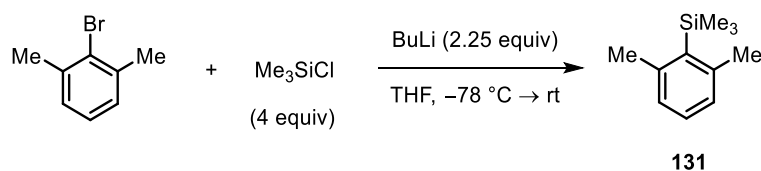
To a nitrogen filled, flame-dried Schlenk flask was added 1-bromo-2-cyclohexylbenzene (0.46 mL, 2.5 mmol) along with dry THF (6 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (2.15 M in hexanes, 2.3 mL, 5.0 mmol) was added dropwise over 15 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 60 mins, then trimethylsilylchloride (0.96 mL, 7.5 mmol) added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (10 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O ( $3 \times 20\text{ mL}$ ). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (401 mg, 69%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.45 (ddd,  $J = 7.5, 1.6, 0.6\text{ Hz}$ , 1H), 7.34 (app. td,  $J = 7.4, 1.5\text{ Hz}$ , 1H), 7.27 (m, 1H), 7.16 (app. td,  $J = 7.3, 1.4\text{ Hz}$ , 1H), 2.73 (tt,  $J = 11.7, 3.2\text{ Hz}$ , 1H), 1.92 – 1.72 (m, 5H), 1.52 – 1.24 (m, 6H), 0.33 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  154.2, 137.7, 134.5, 129.5, 126.0, 125.3, 44.8, 35.0, 27.2, 26.3, 0.6.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 2924 (m), 2850 (w), 1472 (w), 1447 (w), 1247 (m), 1115 (w), 1062 (w), 995 (w), 833 (s), 756 (m), 727 (m), 688 (w), 620 (w), 539 (w), 459 (w).

**HRMS:** Calcd. for C<sub>15</sub>H<sub>24</sub>Si: 232.1642 [M]<sup>+</sup>; found (EI<sup>+</sup>): 232.1645



### (2,6-Dimethylphenyl)trimethylsilane (131)

To a nitrogen filled, flame-dried Schlenk flask was added 1-bromo-2,6-dimethylbenzene (0.99 mL, 7.5 mmol) followed by dry, degassed THF (20 mL) and trimethylsilylchloride (3.79 mL, 30.0 mmol). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (8.05 mL, 18.8 mmol, 2.33 M in hexanes) was added dropwise over 30 minutes. The flask was allowed to gradually return to room temperature overnight (approximately 14 hours). Water (15 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O ( $3 \times 20\text{ mL}$ ). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a colourless oil (234 mg, 18%) along with an amount of recovered 1-bromo-2,6-dimethylbenzene (530 mg, 38%).

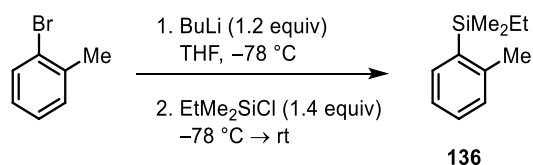
*Note: Attempts to synthesise the compound by addition of BuLi to the bromoarene resulted in consistent formation of material contaminated with 2-butyl-1,3-dimethylbenzene which was inseparable from the desired compound by chromatography and fractional distillation.*

**<sup>1</sup>H (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.13 (t,  $J = 7.6\text{ Hz}$ , 1H), 6.97 (d,  $J = 7.6\text{ Hz}$ , 2H), 2.45 (s, 6H), 0.40 (s, 9H).

**<sup>13</sup>C (100 MHz, CDCl<sub>3</sub>):**  $\delta$  144.3, 136.9, 128.9, 128.2, 25.0, 3.7.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 2952 (w), 2898 (w), 1586 (w), 1443 (w), 1400 (w), 1377 (w), 1325 (w), 1250 (m), 1130 (w), 1059 (w), 1026 (w), 835 (m), 765 (m), 714 (m), 680 (w), 638 (m).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>7</sup>



### (2-Methylphenyl)ethyldimethylsilane (136)

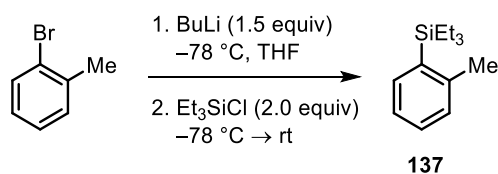
A 25 mL RBF fitted with a stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> through an inlet needle. 2-Bromotoluene (0.60 mL, 5.0 mmol) and dry THF (12 mL) were added *via* syringe and the stirred solution cooled to  $-78\text{ }^{\circ}\text{C}$  in an acetone-dry ice bath. BuLi (2.5 M, 2.4 mL, 6.0 mmol) was added dropwise over 10 minutes, then the solution stirred for an additional 30 minutes at  $-78\text{ }^{\circ}\text{C}$ . Chloro(dimethyl)ethyldisilane (0.75 mL, 7.0 mmol) was added in one portion, and the reaction mixture allowed to return to room temperature overnight. After 14 hours, H<sub>2</sub>O (10 mL) and Et<sub>2</sub>O (10 mL) were added, the layers separated, and the aqueous phase extracted with Et<sub>2</sub>O ( $3 \times 10\text{ mL}$ ). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (0.60 g, 68%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.46 (d,  $J = 7.0\text{ Hz}$ , 1H), 7.30 – 7.23 (m, 1H), 7.20 – 7.12 (m, 2H), 2.46 (s, 3H), 1.00 – 0.93 (m, 3H), 0.87 – 0.78 (m, 2H), 0.32 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  143.8, 137.6, 134.8, 129.9, 129.2, 125.0, 23.2, 7.9, 7.7, -2.2.

**$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ :** 2953 (w), 2911 (w), 2873 (w), 1507 (w), 1471 (w), 1456 (w), 1435 (w), 1417 (w), 1248 (m), 1127 (w), 1078 (w), 1008 (w), 957 (w), 817 (m), 798 (w), 773 (m), 739 (m), 719 (w), 696 (m), 667 (w), 607 (w), 438 (w).

**HRMS** calcd. For C<sub>11</sub>H<sub>18</sub>Si: 178.1172 [M]<sup>+</sup>; found (EI<sup>+</sup>): 178.1176



### (2-Methylphenyl)triethylsilane (137)

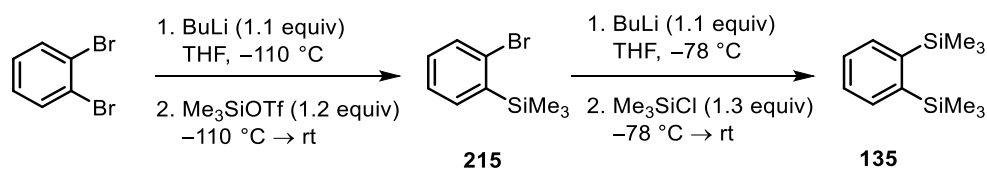
A Schlenk tube equipped with magnetic stirrer bar was flame-dried, then evacuated and backfilled with N<sub>2</sub> three times. 2-Bromotoluene (0.65 mL, 5.0 mmol) and THF (12 mL) were added sequentially *via* syringe, stirring commenced, and the temperature adjusted to  $-78\text{ }^{\circ}\text{C}$  in an acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 3 mL, 7.5 mmol) was added dropwise over approximately 15 mins, then the mixture stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 30 mins. Triethylsilyl chloride (1.65 mL, 10.0 mmol) was added in one portion and the reaction allowed to return to room temperature overnight. After 13 hours the reaction was quenched by the addition of H<sub>2</sub>O (10 mL) and extracted into Et<sub>2</sub>O ( $3 \times 10\text{ mL}$ ). The combined organic extracts were dried over MgSO<sub>4</sub>, and the solvent removed under reduced pressure. The residue was purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (0.84 g, 81%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.47 – 7.42 (m, 1H), 7.31 – 7.23 (m, 1H), 7.20 – 7.12 (m, 2H), 2.44 (s, 3H), 0.99 – 0.92 (m, 9H), 0.90 – 0.82 (m, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  144.0, 135.6, 135.5, 129.9, 129.1, 124.9, 23.2, 7.7, 4.2.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 2952 (m), 2909 (w), 2873 (w), 1456 (w), 1436 (w), 1417 (w), 1236 (w), 1127 (w), 1077 (w), 1002 (m), 970 (w), 802 (w), 722 (m), 709 (m), 669 (w), 600 (w), 586 (w), 442 (w), 419 (w).

**HRMS** calcd. For C<sub>13</sub>H<sub>22</sub>Si: 206.1485 [M]<sup>+</sup>; found (EI<sup>+</sup>): 206.1477



### (2-Bromophenyl)trimethylsilane (215)

To a nitrogen filled, flame-dried, three-necked RBF (fitted with thermometer, suba seal, and connected to manifold) was added 1,2-dibromobenzene (1.20 mL, 10.0 mmol) along with dry THF (15 mL). The solution was cooled to  $-110\text{ }^\circ\text{C}$  in an ethanol/liquid nitrogen bath and *n*-butyllithium (2.08 M in hexanes, 5.30 mL, 11.0 mmol) was added dropwise over 60 minutes. The mixture was stirred at  $-110\text{ }^\circ\text{C}$  for a further 30 mins, then trimethylsilyltriflate (2.20 mL, 12.0 mmol) was added slowly *via* syringe such that the temperature remained below  $-100\text{ }^\circ\text{C}$ . The flask was allowed to slowly return to room temperature overnight. Water (10 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O ( $3 \times 20\text{ mL}$ ). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a colourless oil (1.88 g, 82%).

*Note: Effective control of the internal reaction temperature is crucial, with poor control resulting in significantly diminished product yields.*

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.55 (dd,  $J = 7.8, 1.2\text{ Hz}$ , 1H), 7.46 (dd,  $J = 7.5, 1.9\text{ Hz}$ ), 7.30 (m, 1H), 7.22 (app. td,  $J = 7.5, 1.9\text{ Hz}$ ), 0.42 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  141.1, 136.1, 132.7, 130.7, 130.6, 126.4, 0.6.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 3056 (w), 2953 (w), 2897 (w), 1578 (w), 1553 (w), 1450 (w), 1418 (w), 1406 (w), 1248 (m), 1123 (m), 1103 (w), 1038 (w), 1019 (m), 836 (s), 743 (s), 708 (m), 690 (w), 648 (w), 620 (w), 433 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>5</sup>

### 1,2-Bis(trimethylsilyl)benzene (135)

To a nitrogen filled, flame-dried Schlenk flask was added (2-bromophenyl)trimethylsilane (0.72 g, 3.1 mmol) along with dry, degassed THF (10 mL). The solution was cooled to  $-78\text{ }^\circ\text{C}$  and *n*-butyllithium (2.33 M in hexanes, 1.50 mL, 3.5 mmol) was added dropwise over 15 minutes. The mixture was stirred at  $-78\text{ }^\circ\text{C}$  for a further 45 mins, then trimethylsilylchloride

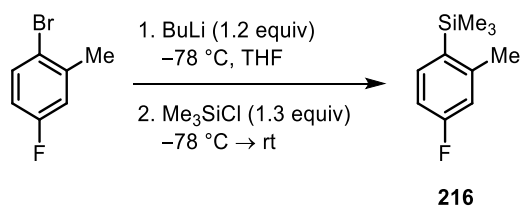
(0.51 mL, 4.0 mmol) added *via* syringe in one portion. The flask was removed from the cold bath and allowed to return to room temperature overnight. H<sub>2</sub>O (10 mL) was added, the layers separated, and the aqueous phase extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (0.49 g, 71%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.70 (dd, *J* = 5.6, 3.3 Hz, 2H), 7.35 (dd, *J* = 5.6, 3.3 Hz, 2H), 0.40 (s, 18H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 146.1, 135.2, 127.8, 1.9.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3044 (w), 2951 (w), 2898 (w), 1449 (w), 1410 (w), 1264 (w), 1247 (m), 1119 (w), 1054 (w), 1039 (w), 831 (s), 753 (m), 735 (m), 682 (m), 658 (w), 620 (w), 439 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>8</sup>



#### (4-Fluoro-2-methylphenyl)trimethylsilane (216)

A 250 mL RBF fitted with a stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> through an inlet needle. 4-Fluoro-2-methylbromobenzene (3.34 mL, 26.5 mmol) and dry THF (60 mL) were added *via* syringe and the stirred solution cooled to −78 °C in an acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 12.0 mL, 30.0 mmol) was added dropwise over 30 minutes, then the solution stirred for an additional 45 minutes at −78 °C. Trimethylsilyl chloride (4.19 mL, 33.0 mmol) was added in one portion, and the reaction mixture allowed to return to room temperature overnight. After 14 hours, H<sub>2</sub>O (50 mL) and Et<sub>2</sub>O (50 mL) were added, the layers separated, and the aqueous phase extracted with Et<sub>2</sub>O (3 × 50 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: hexanes) to afford the title compound as a clear, colourless oil (4.59 g, 95%).

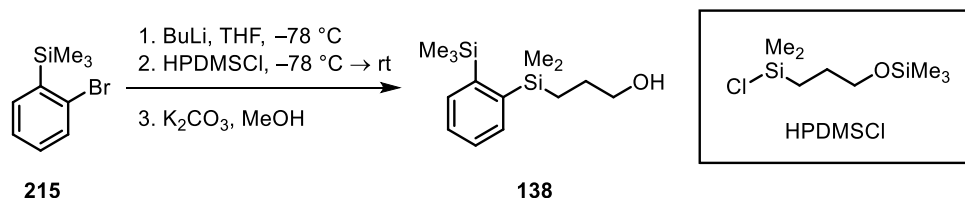
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.45 – 7.36 (app t, *J* = 7.3 Hz, 1H), 6.92 – 6.84 (m, 2H), 2.46 (s, 3H), 0.32 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 163.8 (d, *J* = 247.4 Hz), 146.4 (d, *J* = 7.1 Hz), 136.2 (d, *J* = 7.6 Hz), 134.0 (d, *J* = 3.5 Hz), 116.8 (d, *J* = 19.3 Hz), 111.8 (d, *J* = 19.0 Hz), 23.1 (d, *J* = 2.0 Hz), 0.0.

**<sup>19</sup>F NMR (375 MHz, CDCl<sub>3</sub>):** δ –113.48 (m)

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2956 (w), 1578 (m), 1482 (w), 1248 (m), 1221 (m), 1068 (m), 949 (m), 834 (s), 757 (m), 706 (w), 477 (w), 445 (w).

<sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR data are consistent with those reported in the literature.<sup>4</sup>



### 3-{[Dimethyl[2-(trimethylsilyl)phenyl]silyl]propyl}propan-1-ol (138)

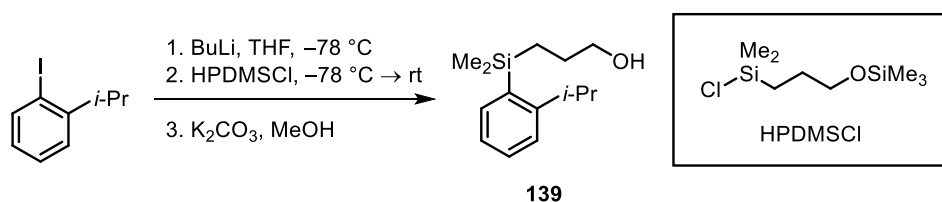
To a nitrogen filled, flame-dried Schlenk flask was added (2-bromophenyl)trimethylsilane (0.72 g, 3.1 mmol) along with dry, degassed THF (10 mL). The solution was cooled to –78 °C and *n*-butyllithium (2.33 M in hexanes, 1.50 mL, 3.5 mmol) was added dropwise over 15 minutes. The mixture was stirred at –78 °C for a further 45 mins, then HPDMSCl (0.91 mL, 0.84 g, 3.75 mmol) added *via* syringe in one portion. The flask was removed from the cold bath and allowed to return to room temperature overnight (ca. 14 hours). The volatiles were removed under vacuum, then the remaining residue dissolved in methanol (10 mL) and K<sub>2</sub>CO<sub>3</sub> (1.24 g, 9.0 mmol) added. The mixture was stirred for 4 hours, by which time the reaction appeared complete by TLC (eluent: 3:1 hexanes/EtOAc). Water (25 mL) and EtOAc (30 mL) were added and the layers separated, then the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, and concentrated in *vacuo*. The resulting oil was purified by column chromatography (eluent: 3:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (241 mg, 29%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.66 (m, 2H), 7.32 (m, 2H), 3.60 (t, *J* = 6.8 Hz, 2H), 1.58 (m, 2H), 0.83 (m, 2H), 0.38 (s, 6H), 0.37 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 146.4, 144.8, 135.5, 135.5, 128.0, 127.9, 65.9, 27.6, 13.3, 2.2, 0.2.

**v<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3305 (br), 2948 (w), 1263 (w), 1247 (m), 1118 (w), 1053 (m), 1039 (w), 1011 (w), 832 (m), 737 (m), 682 (m), 659 (w), 621 (w).

**HRMS:** Calcd. for C<sub>14</sub>H<sub>26</sub>ONaSi<sub>2</sub>: 289.1414 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 289.1420



### 3-{Dimethyl[2-(propan-2-yl)phenyl]silyl}propan-1-ol (**139**)

To a nitrogen filled, flame-dried Schlenk flask was added 1-iodo-2-*iso*-propylbenzene (0.50 mL, 3.1 mmol) along with dry, degassed THF (10 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (2.33 M in hexanes, 1.50 mL, 3.5 mmol) was added dropwise over 15 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 45 mins, then HPDMSiCl (0.91 mL, 0.84 g, 3.75 mmol) added *via* syringe in one portion. The flask was removed from the cold bath and allowed to return to room temperature overnight (ca. 14 hours). The volatiles were removed under vacuum, then the remaining residue dissolved in methanol (10 mL) and K<sub>2</sub>CO<sub>3</sub> (1.24 g, 9.0 mmol) added. The mixture was stirred for 4 hours, by which time the reaction appeared complete by TLC (eluent: 3:1 hexanes/EtOAc). Water (25 mL) and EtOAc (30 mL) were added and the layers separated, then the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, and concentrated in *vacuo*. The resulting oil was purified by column chromatography (eluent: 3:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (105 mg, 14%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.42 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.28 (m, 2H), 7.16 (app. td, *J* = 7.2, 1.5 Hz, 1H), 3.60 (t, *J* = 6.8 Hz, 2H), 3.11 (hept, *J* = 6.8 Hz, 1H), 1.65 – 1.50 (m, 2H), 1.32 – 1.19 (m, 7H), 0.86 – 0.77 (m, 2H), 0.34 (s, 6H).

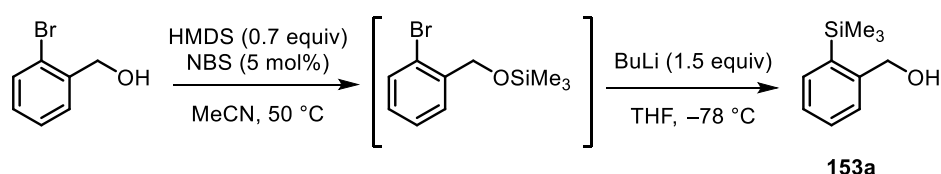
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.2, 135.8, 134.6, 129.6, 125.2, 125.2, 65.8, 33.8, 27.5, 24.7, 12.3,  $-1.3$ .



$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3311 (br), 2960 (w), 2929 (w), 2868 (w), 1474 (w), 1458 (w), 1432 (w), 1415 (w), 1383 (w), 1362 (w), 1249 (w), 1117 (w), 1065 (w), 1052 (w), 1029 (w), 1011 (w), 863 (w), 832 (m), 813 (m), 764 (m), 730 (m), 704 (w), 685 (w), 630 (w), 548 (w), 461 (w).

**HRMS:** Calcd. for  $\text{C}_{14}\text{H}_{24}\text{ONaSi}$ : 259.1489  $[\text{M}+\text{Na}]^+$ ; found (ESI<sup>+</sup>): 259.1496

#### 5.4.2 Preparation of coordinating *ortho*-Substituted Arylsilanes



#### [2-(Trimethylsilyl)phenyl]methanol (**153a**)

*Note: The NBS catalysed silylation reaction was based on a literature procedure.<sup>9</sup>*

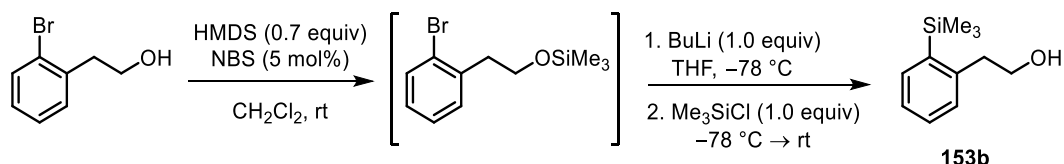
2-Bromobenzyl alcohol (1.87 g, 10.0 mmol) was added to a flame-dried,  $\text{N}_2$ -purged 100 mL RBF containing a magnetic stirrer bar, and fitted with a rubber septum and inlet needle. MeCN (25 mL) was added *via* syringe, followed by hexamethyldisilazane (HMDS, 1.47 mL, 7.0 mmol). The resulting solution was stirred for 15 mins at room temperature, then *N*-bromosuccinimide (NBS, 90 mg, 0.5 mmol) added in one portion. The temperature was adjusted to 50 °C and stirring maintained for a further 2 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (10 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried,  $\text{N}_2$ -purged 100 mL RBF (again fitted with a septum and inlet needle). THF (20 mL) was added, and the solution cooled to -78 °C in an acetone-dry ice bath. *n*-Butyllithium (1.6 M in hexanes, 6.9 mL, 11.0 mmol) was added by syringe over approximately 15 minutes, and the solution allowed to return to room temperature overnight. After 14 hours, the mixture was quenched by the addition of  $\text{H}_2\text{O}$  (10 mL) and extracted into  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated *in vacuo*, and the resulting crude oil purified by column chromatography (eluent: 4:1 hexanes/ $\text{EtOAc}$ ) to afford the title compound as a viscous, colourless oil (1.44 g, 86%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.54 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.47 (ddd, *J* = 7.6, 1.3, 0.6 Hz, 1H), 7.40 (app. td, *J* = 7.5, 1.5 Hz, 1H), 7.29 (app. td, *J* = 7.4, 1.4 Hz, 1H), 4.78 (d, *J* = 5.2 Hz, 2H), 0.35 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 146.6, 138.6, 135.2, 130.0, 128.2, 127.5, 65.9, 0.8.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3287 (w, br), 2952 (w), 2895 (w), 1434 (w), 1407 (w), 1247 (m), 1200 (m), 1125 (w), 1078 (w), 1010 (w), 834 (s), 743 (m), 728 (m), 687 (m), 622 (m), 604 (w), 460 (w), 429 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>10</sup>



## 2-[2-(Trimethylsilyl)phenyl]ethanol (153b)

*Note: The NBS catalysed silylation reaction was based on a literature procedure.<sup>9</sup>*

2-Bromophenethyl alcohol (5.0 g, 24.9 mmol) was added to a flame-dried, N<sub>2</sub>-purged 250 mL RBF equipped with a magnetic stirrer bar, and fitted with a rubber septum and inlet needle. MeCN (60 mL) was added *via* syringe, followed by hexamethyldisilazane (HMDS, 3.65 mL, 17.4 mmol). The resulting solution was stirred for 10 mins at room temperature, then *N*-bromosuccinimide (NBS, 220 mg, 1.3 mmol, 5 mol%) added in one portion. The temperature was adjusted to 50 °C and stirring maintained for a further 2 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (30 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, 250 mL RBF (again fitted with a septum and inlet needle). THF (40 mL) was added, and the solution cooled to -78 °C in an acetone-dry ice bath. *n*-Butyllithium (1.6 M in hexanes, 14.0 mL, 22.5 mmol) was added by syringe over approximately 15 minutes, and the solution stirred at this temperature for 1 hour. Trimethylsilyl chloride (3.2 mL, 25.0 mmol) was then added *via* syringe and the reaction mixture allowed to return to room temperature overnight. After 14 hours, the mixture was quenched by the addition of H<sub>2</sub>O (20 mL), and extracted into Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were washed with HCl (0.1 M, 25 mL), then H<sub>2</sub>O (25 mL), dried over MgSO<sub>4</sub>,

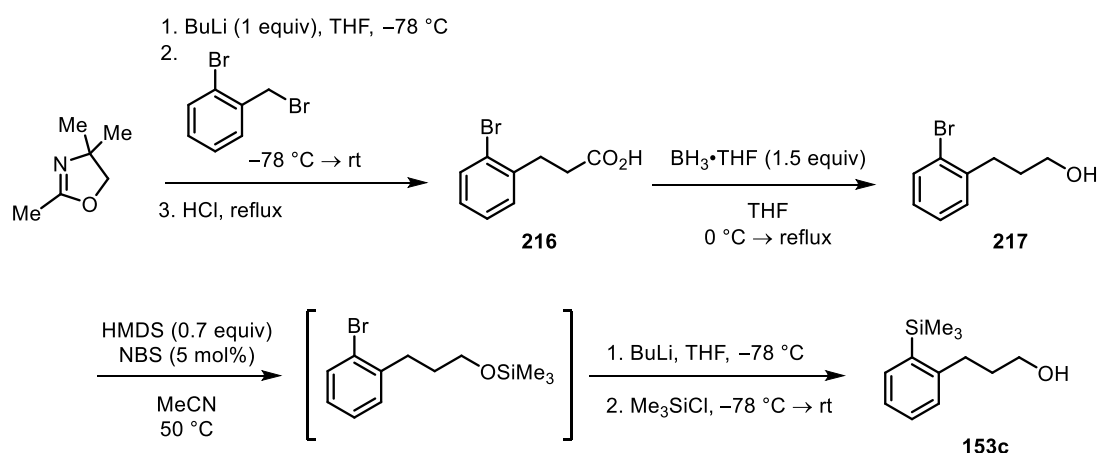
concentrated *in vacuo*, and the resulting crude oil purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a viscous, colourless oil (3.14 g, 65%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.51 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.33 (app. td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (m, 2H), 3.87 (m, 2H), 3.02 (t, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 5.7 Hz, 1H), 0.35 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.9, 139.3, 135.1, 129.4, 129.2, 125.9, 64.3, 39.3, 0.7.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3327 (br, w), 2952 (w), 2894 (w), 1471 (w), 1429 (w), 1248 (m), 1124 (w), 1079 (w), 1040 (m), 833 (s), 751 (m), 726 (m), 687 (m), 621 (m), 579 (w), 456 (w), 422 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>11</sup>



### 3-(2-Bromophenyl)propionic acid (216)

Prepared according to the following modified literature procedure:<sup>12</sup>

A 250 mL RBF equipped with a stirrer bar and rubber septum was flame-dried then evacuated and backfilled with N<sub>2</sub> four times. 2,4,4-Trimethyl-2-oxazoline (4.5 mL, 35.0 mmol) and THF (100 mL) were added *via* syringe, and the stirred solution cooled to -78 °C in a dry ice-acetone bath. *n*-Butyllithium (2.15 M in hexanes, 16.3 mL, 35.0 mmol) was added dropwise over 30 minutes, and the mixture stirred for a further 30 minutes at -78 °C. 2-Bromobenzyl bromide (8.7 g, 35.0 mmol) was added in one portion *via* syringe and the solution warmed to room temperature over 2 hours. H<sub>2</sub>O (5 mL) was added to quench any remaining organolithium reagent and the solvent removed under reduced pressure. Et<sub>2</sub>O (100 mL) was added and the mixture extracted with 10 % w/w HCl (5 × 75 mL). The aqueous extracts were combined and

the pH adjusted to ~11 with 40% w/w NaOH. The batch was split into two roughly equal 300 mL portions, and both were extracted into Et<sub>2</sub>O (5 × 100 mL). The combined extracts were dried *in vacuo*, then the resulting oil dissolved in 10% w/w HCl (100 mL) and heated under reflux for 45 minutes. The cooled suspension was extracted into Et<sub>2</sub>O (5 × 40 mL), and the combined organic extracts washed with 10% w/w NaOH (5 × 40 mL). The aqueous washings were combined and acidified by cautious addition of HCl, then extracted into Et<sub>2</sub>O (5 × 50 mL). Removal of the solvent under reduced pressure and recrystallisation from hot CH<sub>2</sub>Cl<sub>2</sub> afforded the title compound as a white, crystalline solid (3.44 g, 43%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.55 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.12 – 7.07 (m, 1H), 3.08 (t, *J* = 7.8 Hz, 2H), 2.72 (t, *J* = 7.7 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 177.9, 139.5, 133.1, 130.6, 128.4, 127.8, 124.5, 33.8, 31.3.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2904 (br), 1696 (m), 1470 (w), 1435 (m), 1406 (w), 1367 (w), 1317 (m), 1268 (m), 1215 (m), 1023 (m), 949 (m), 928 (m), 783 (m), 749 (s), 700 (w), 686 (m), 652 (m), 575 (w), 522 (w), 434 (m).

**mp:** 98 – 100 °C (CH<sub>2</sub>Cl<sub>2</sub>); lit. 99 – 100 °C.<sup>12</sup>

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>13</sup>

### 3-(2-Bromophenyl)propan-1-ol (217)

A two-necked 250 mL RBF equipped with stirrer bar, condenser and rubber septum was flame-dried then purged with N<sub>2</sub> through an inlet needle for 30 minutes. 3-(2-Bromophenyl)propionic acid (5.0 g, 21.8 mmol) was added followed by dry THF (120 mL) and stirring commenced. The solution was cooled to 0 °C in an ice bath, and BH<sub>3</sub>·THF (1.0 M, 30.0 mL, 30.0 mmol) added by syringe over 30 minutes (*Note: a significant amount of H<sub>2</sub> gas was evolved*). The cold bath was removed and the mixture refluxed for 1 hour, then cooled to 0 °C and quenched by the careful addition of H<sub>2</sub>O (~10 mL). The volatiles were removed under reduced pressure and the remaining residue dissolved in Et<sub>2</sub>O (50 mL) then washed with saturated Na<sub>2</sub>CO<sub>3</sub> (3 × 50 mL), dried over MgSO<sub>4</sub>, and concentrated to afford the title compound as a colourless, viscous oil without the need for additional purification (3.70g, 79%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.53 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.10 – 7.05 (m, 1H), 3.71 (t, *J* = 6.4 Hz, 2H), 2.87 – 2.81 (m, 2H), 1.95 – 1.85 (m, 2H), 1.58 (br s, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 141.2, 133.0, 130.6, 127.8, 127.6, 124.6, 62.3, 32.9, 32.5.

**$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ :** 3308 (br w), 2936 (w), 2864 (w), 1471 (w), 1455 (w), 1436 (w), 1054 (m), 1019 (m), 914 (w), 746 (m), 699 (m), 657 (w), 594 (w), 579 (w), 445 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>13</sup>

### **3-(2-Trimethylsilylphenyl)propan-1-ol (153c)**

*Note: The NBS catalysed silylation reaction was based on a literature procedure.<sup>9</sup>*

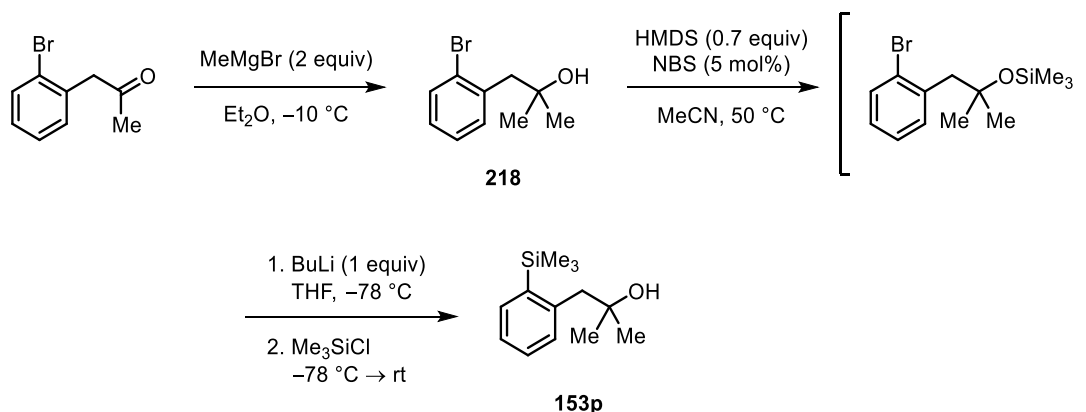
A 100 mL RBF equipped with stirrer bar and rubber septum was flame-dried then purged with N<sub>2</sub> through an inlet needle. 3-(2-Bromophenyl)propanol (3.70 g, 17.2 mmol), MeCN (40 mL), and hexamethyldisilazane (HMDS, 2.54 mL, 12.1 mmol) were added *via* syringe (in that order) and stirring commenced. The reaction temperature was adjusted to 50 °C, then *N*-bromosuccinimide (NBS, 0.15 g, 0.9 mmol, 5 mol%) added in one portion. Stirring was maintained for 2 hours, then the solution allowed to return to room temperature over 30 minutes. The solution was concentrated under reduced pressure, and the residue dissolved in hexane (25 mL) then passed through a short pad of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, 100 mL RBF (again fitted with rubber septum and inlet needle). THF (30 mL) was added, and the solution cooled to −78 °C in an acetone-dry ice bath. *n*-Butyllithium (1.6 M in hexanes, 9.4 mL, 15.0 mmol) was added by syringe over approximately 15 minutes, and the solution stirred at this temperature for 1 hour. Trimethylsilyl chloride (2.2 mL, 17.5 mmol) was then added *via* syringe and the reaction mixture allowed to return to room temperature overnight. After 14 hours, the mixture was quenched by the addition of H<sub>2</sub>O (20 mL) and extracted into Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were washed with HCl (0.1 M, 25 mL), then H<sub>2</sub>O (25 mL), dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the resulting crude oil purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a viscous, colourless oil (1.96 g, 75%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.49 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.32 (app. td, *J* = 7.5, 1.5 Hz, 1H), 7.25 – 7.16 (m, 2H), 3.80 – 3.72 (m, 2H), 2.85 – 2.78 (m, 2H), 1.95 – 1.86 (m, 2H), 1.36 (br s, 1H), 0.34 (s 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  147.8, 138.3, 134.8, 129.4, 128.7, 125.3, 62.9, 35.4, 32.5, 0.6.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3314 (br w), 2951 (w), 2896 (w), 2869 (w), 1471 (w), 1433 (w), 1260 (w), 1248 (m), 1124 (w), 1057 (w), 834 (s), 751 (m), 726 (m), 687 (w), 621 (w), 471 (w), 455 (w).

**HRMS:** Calcd. for  $\text{C}_{12}\text{H}_{20}\text{ONaSi}$ : 231.1176  $[\text{M}+\text{Na}]^+$ ; found (ESI<sup>+</sup>): 231.1173



#### 1-(2-Bromophenyl)-2-methyl-propan-2-ol (**218**)

A 250 mL three-necked RBF equipped with magnetic stirrer bar and fitted with a low temperature thermometer and rubber septum was flame-dried, then purged with  $\text{N}_2$  through an inlet needle. 1-(2-Bromophenyl)propanone (2.24 mL, 15.0 mmol) and dry  $\text{Et}_2\text{O}$  (150 mL) were added by syringe and stirring commenced. The solution was cooled to  $-15\text{ }^\circ\text{C}$  in an ice-salt bath, then  $\text{MeMgBr}$  (3.0 M in  $\text{Et}_2\text{O}$ , 7.5 mL, 22.5 mmol) was added dropwise over approximately 30 minutes (ensuring that the internal temperature did not exceed  $-10\text{ }^\circ\text{C}$ ). The solution was warmed slightly to  $0\text{ }^\circ\text{C}$  and stirred for a further 3 hours. The reaction mixture was then poured into a mixture of ice (approx. 100 g) and sat.  $\text{NH}_4\text{Cl}$  (50 mL). The resulting biphasic solution was transferred to a separating funnel, and the aqueous layer extracted with  $\text{EtOAc}$  ( $3 \times 100\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated *in vacuo*, and the residue purified by column chromatography (eluent: 4:1 hexanes/ $\text{EtOAc}$ ) to afford the title compound as a clear, colourless oil (2.74 g, 80%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):** 7.60 (dd,  $J = 8.0, 1.3\text{ Hz}$ , 1H), 7.38 (dd,  $J = 7.6, 1.8\text{ Hz}$ , 1H), 7.32 – 7.24 (m, 1H), 7.12 (ddd,  $J = 8.0, 7.3, 1.8\text{ Hz}$ , 1H), 3.04 (s, 2H), 1.52 (br s, 1H), 1.31 (s, 6H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):** 137.8, 133.2, 132.5, 128.2, 127.2, 126.1, 72.0, 48.1, 29.6.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3393 (br w), 2970 (w), 2924 (w), 1469 (w), 1436 (w), 1375 (w), 1205 (w), 1137 (m), 1099 (w), 1024 (m), 970 (w), 902 (w), 771 (m), 743 (w), 659 (w), 612 (w), 530 (w).

$^1\text{H}$  and  $^{13}\text{C}$  NMR data are consistent with those reported in the literature.<sup>14</sup>

### 1-(2-(Trimethylsilyl)phenyl)-2-methyl-propan-2-ol (153p)

*Note: The NBS catalysed silylation reaction was based on a literature procedure.*<sup>9</sup>

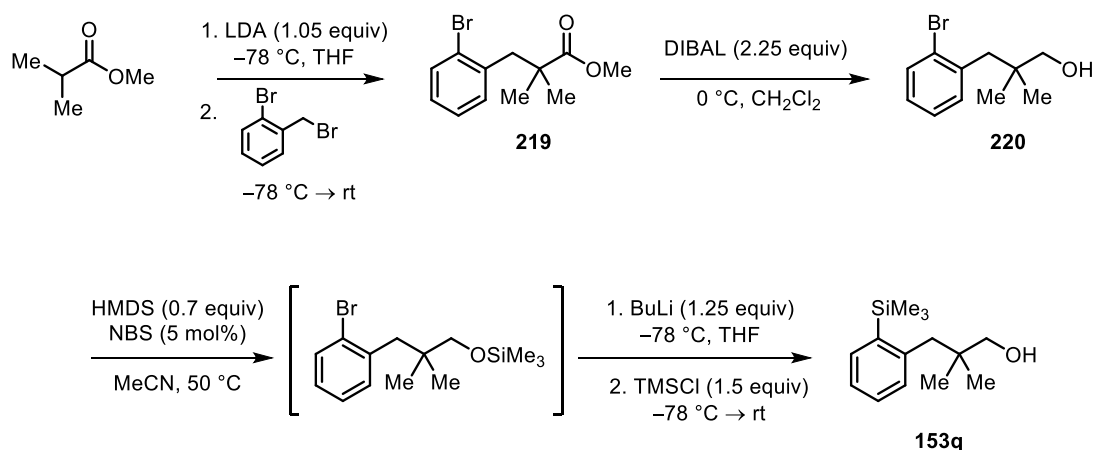
1-(2-bromophenyl)-2-methyl-propan-2-ol (2.70 g, 11.8 mmol) was added to a flame-dried,  $\text{N}_2$ -purged, 100 mL RBF containing a magnetic stirrer bar, and fitted with a rubber septum and inlet needle. MeCN (30 mL) was added *via* syringe, followed by hexamethyldisilazane (HMDS, 1.74 mL, 8.3 mmol). The resulting solution was stirred for 15 mins at room temperature, then *N*-bromosuccinimide (NBS, 105 mg, 0.6 mmol) added in one portion. The temperature was adjusted to 50 °C and stirring maintained for a further 3 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (10 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried,  $\text{N}_2$ -purged, 100 mL RBF (again fitted with a septum and inlet needle). THF (40 mL) was added, and the solution cooled to -78 °C in an acetone-dry ice bath. *n*-Butyllithium (2.3 M in hexanes, 5.2 mL, 12.0 mmol) was added by syringe over approximately 15 minutes, and the solution stirred at -78 °C for 1 hour. Trimethylsilyl chloride (1.63 mL, 15.0 mmol) was added *via* syringe and the resulting solution allowed to return to room temperature overnight. After 14 hours, the mixture was quenched by the addition of  $\text{H}_2\text{O}$  (20 mL), and extracted into  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL). The combined organic extracts were washed with HCl (10% w/w, 30 mL), then brine (25 mL) dried over  $\text{MgSO}_4$ , concentrated *in vacuo*, and the resulting crude oil purified by column chromatography (eluent: 9:1 hexanes/ $\text{EtOAc}$ ) to afford the title compound as a viscous, pale yellow oil (0.87 g, 33%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.53 (ddd,  $J = 7.5, 1.6, 0.6$  Hz, 1H), 7.40 (ddd,  $J = 7.7, 1.4, 0.6$  Hz, 1H), 7.31 (app. td,  $J = 7.6, 1.6$  Hz, 1H), 7.23 (app. td,  $J = 7.3, 1.4$  Hz, 1H), 2.95 (s, 2H), 1.27 (s, 1H), 1.26 (s, 6H), 0.34 (s, 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  143.6, 140.5, 135.3, 130.6, 128.8, 125.9, 71.3, 48.3, 30.1, 1.5.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 2964 (w), 1247 (m), 1131 (w), 834 (s), 755 (w), 738 (m), 682 (w), 622 (w).

HRMS: Calcd. for  $\text{C}_{13}\text{H}_{22}\text{ONaSi}$ : 245.1332  $[\text{M}+\text{Na}]^+$ ; found (ESI<sup>+</sup>): 245.1333



### Methyl 3-(2-bromophenyl)-2,2-dimethylpropanoate (**219**)

A 250 mL RBF equipped with magnetic stirrer and rubber septum was flame-dried and purged under a stream of  $\text{N}_2$  through an inlet needle. THF (75 mL) then LDA (2.0 M in THF, 27.5 mL, 55.0 mmol) were added *via* syringe and stirring commenced. The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  in an acetone-dry ice bath, then methyl isobutyrate (6.02 mL, 52.5 mmol) added dropwise over approximately 15 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 1 hour, then 2-bromobenzyl bromide (7.31 mL, 55.0 mmol) added in one portion. The mixture was allowed to return to room temperature overnight. After 16 hours the reaction was quenched by addition of  $\text{H}_2\text{O}$  (50 mL) and extracted into  $\text{Et}_2\text{O}$  ( $3 \times 50\text{ mL}$ ). The combined organic extracts were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The crude oil was purified by column chromatography (eluent: 100:0  $\rightarrow$  80:20 hexane/ $\text{EtOAc}$ ) to afford the title compound as a pale yellow oil that crystallised to a waxy solid on standing for a number of days (12.69 g, 89%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):** 7.54 (dd,  $J = 8.0, 1.3\text{ Hz}$ , 1H), 7.20 (app. td,  $J = 7.5, 1.3\text{ Hz}$ , 1H), 7.13 (app. td,  $J = 7.7, 1.9\text{ Hz}$ , 1H), 7.06 (dd,  $J = 7.7, 1.8\text{ Hz}$ , 1H), 3.69 (s, 3H), 3.12 (s, 2H), 1.24 (s, 6H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):** 178.0, 137.9, 133.2, 131.5, 128.2, 127.2, 126.2, 52.0, 44.4, 44.4, 25.1.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2986 (w), 2967 (w), 2943 (w), 2873 (w), 1726 (s), 1468 (m), 1433 (m), 1390 (m), 1370 (w), 1324 (m), 1279 (m), 1188 (m), 1177 (m), 1131 (s), 1103 (m), 1050 (w), 1019



(m), 992 (m), 962 (m), 942 (w), 902 (w), 860 (w), 807 (w), 770 (w), 747 (s), 717 (w), 661 (m), 601 (w), 592 (w), 453 (w).

**HRMS:** Calcd. for  $C_{12}H_{15}O_2^{79}Br$ : 270.0250  $[M]^+$ ; found ( $EI^+$ ): 270.0242

### 3-(2-Bromophenyl)-2,2-dimethylpropan-1-ol (220)

A 250 mL RBF equipped with magnetic stirrer and rubber septum was flame-dried and purged with a stream of  $N_2$  through an inlet needle. Methyl 3-(2-bromophenyl)2,2-dimethylpropanoate (4.88 g, 18.0 mmol) was added followed by  $CH_2Cl_2$  (35 mL) and stirring commenced. Once the solid had fully dissolved, the temperature was adjusted to 0 °C in an ice-water bath. DIBAL (1.0 M in hexanes, 40.5 mL, 40.5 mmol) was added dropwise over 30 minutes, and the resulting mixture allowed to stir at 0 °C for 4 hours. The reaction was carefully quenched by addition of MeOH (5 mL) then a saturated solution of Rochelle's Salt (50 mL) and  $Et_2O$  (50 mL) added sequentially. The mixture was stirred rapidly for 1 hour, then the layers separated and the organic layer washed with sat.  $NH_4Cl$  ( $2 \times 50$  mL) and brine ( $2 \times 50$  mL). The solvent was removed under reduced pressure to afford the title compound as a pale yellow oil without the need for additional purification (4.75 g, quant.).

**$^1H$  NMR (400 MHz,  $CDCl_3$ ):** 7.55 (dd,  $J = 8.0, 1.3$  Hz, 1H), 7.30 – 7.19 (m, 2H), 7.06 (ddd,  $J = 8.0, 7.1, 2.0$  Hz, 1H), 3.37 (d,  $J = 6.1$  Hz, 2H), 2.83 (s, 2H), 0.95 (s, 6H).

**$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):** 138.7, 133.1, 132.7, 127.8, 127.0, 126.1, 71.2, 42.8, 37.9, 24.3.

**$\nu_{max}(neat)/cm^{-1}$ :** 3359 (br w), 2955 (w), 2928 (w), 2868 (w), 1468 (m), 1434 (w), 1384 (w), 1364 (w), 1026 (m), 986 (m), 766 (w), 742 (m), 707 (w), 659 (m), 610 (w).

**HRMS:** Calcd. for  $C_{11}H_{15}O^{79}Br$ : 242.0301  $[M]^+$ ; found ( $EI^+$ ): 242.0311

### 2,2-Dimethyl-3-[2-(trimethylsilyl)phenyl]propan-1-ol (153q)

*Note: The NBS catalysed silylation reaction was based on a literature procedure.<sup>9</sup>*

A 100 mL RBF equipped with stirrer bar and rubber septum was flame-dried then purged with  $N_2$  through an inlet needle. 3-(2-Bromophenyl)-2,2-dimethylpropan-1-ol (4.75 g, 19.5 mmol), MeCN (50 mL), and hexamethyldisilazane (HMDS, 2.93 mL, 14.0 mmol) were added *via* syringe (in that order) and stirring commenced. The reaction temperature was adjusted to

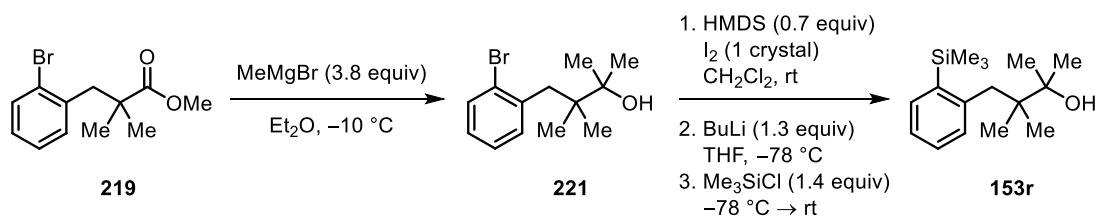
50 °C, then *N*-bromosuccinimide (NBS, 0.18 g, 1.0 mmol, 5 mol%) added in one portion. Stirring was maintained for 2 hours, then the solution allowed to return to room temperature over 30 minutes. The solution was concentrated under reduced pressure, and the residue dissolved in hexane (25 mL) then passed through a short pad of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, 250 mL RBF (again fitted with rubber septum and inlet needle). THF (50 mL) was added, and the solution cooled to –78 °C in an acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 10 mL, 25.0 mmol) was added by syringe over approximately 15 minutes, and the solution stirred at this temperature for 1 hour. Trimethylsilyl chloride (3.5 mL, 27.5 mmol) was then added via syringe and the reaction mixture allowed to return to room temperature overnight. After 18 hours, the mixture was quenched by the addition of H<sub>2</sub>O (20 mL) and extracted into Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were washed with HCl (10% w/w, 40 mL), then H<sub>2</sub>O (40 mL), dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the resulting oil purified by column chromatography (eluent: 4:1 hexanes/EtOAc) to yield the title compound as a viscous, colourless oil (3.24 g, 70%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 – 7.51 (m, 1H), 7.34 – 7.26 (m, 2H), 7.25 – 7.17 (m, 1H), 3.45 (s, 2H), 2.81 (s, 2H), 0.93 (s, 6H), 0.37 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 145.1, 140.1, 135.2, 130.3, 128.5, 125.4, 72.1, 43.3, 37.1, 24.7, 1.8.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3332 (br), 2952 (w), 2897 (w), 2869 (w), 1470 (w), 1433 (w), 1261 (w), 1248 (m), 1112 (w), 1037 (m), 834 (m), 774 (w), 756 (w), 737 (m), 683 (w), 622 (w).

**HRMS:** Calcd. for C<sub>14</sub>H<sub>24</sub>ONaSi: 259.1489 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 259.1492



#### 4-(2-Bromophenyl)-2,3,3-trimethylbutan-2-ol (221)

A 250 mL three-necked RBF equipped with magnetic stirrer bar and fitted with a low temperature thermometer and rubber septum was flame-dried, then purged with N<sub>2</sub> through an

inlet needle. Methyl 3-(2-bromophenyl)-2,2-dimethylpropanoate (4.88 g, 18.0 mmol) and dry Et<sub>2</sub>O (150 mL) were added by syringe and stirring commenced. The solution was cooled to -15 °C in an ice-salt bath, then MeMgBr (3.0 M in Et<sub>2</sub>O, 13.3 mL, 40.0 mmol) was added dropwise over approximately 30 minutes (ensuring that the internal temperature did not exceed -10 °C). The solution was warmed slightly to 0 °C and stirred for a further 4 hours. Crude <sup>1</sup>H NMR indicated incomplete consumption of the starting material, so the crude reaction mixture was re-subjected to the reaction conditions and further MeMgBr (3.0 M in Et<sub>2</sub>O, 9.3 mL, 27.9 mmol) added. After stirring at room temperature for a further 4 hours, the reaction mixture was poured into a mixture of ice (approx. 100 g) and sat. NH<sub>4</sub>Cl (50 mL). The resulting biphasic solution was transferred to a separating funnel, and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the residue purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (4.10 g, 84%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.58 – 7.52 (m, 1H), 7.25 – 7.19 (m, 2H), 7.06 (m, 1H), 2.94 (s, 2H), 1.33 (s, 6H), 0.91 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 139.6, 133.2, 132.9, 127.7, 126.9, 126.7, 75.9, 42.8, 40.9, 25.7, 21.5.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3439 (br, w), 2971 (w), 2876 (w), 1468 (m), 1436 (w), 1368 (w), 1163 (w), 1115 (w), 1085 (w), 1047 (w), 1023 (m), 942 (w), 873 (w), 750 (m), 732 (w), 659 (w).

**HRMS:** Calcd. for C<sub>13</sub>H<sub>19</sub>O<sup>79</sup>BrNa: 293.0512 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 293.0525

### 2,3,3-Trimethyl-4-[2-(trimethylsilyl)phenyl]butan-2-ol (153r)

*Note: The iodine-catalysed silylation reaction used is based on a literature procedure.*<sup>15</sup>

A 100 mL RBF equipped with stirrer bar and rubber septum was flame-dried then purged with N<sub>2</sub> through an inlet needle. 4-(2-Bromophenyl)-2,3,3-trimethylbutan-2-ol (4.00 g, 14.7 mmol), CH<sub>2</sub>Cl<sub>2</sub> (20 mL), and hexamethyldisilazane (HMDS, 2.16 mL, 10.3 mmol) were added *via* syringe (in that order) and stirring commenced. A single crystal of iodine was added, then stirring was maintained at room temperature for 15 minutes. Solid Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (approx. 3 g) was added and the reaction mixture stirred for a further 30 minutes, then passed through a short pad of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, 150 mL RBF (again fitted with rubber septum and inlet needle). THF (40 mL) was added, and the solution cooled to -78 °C in an acetone-

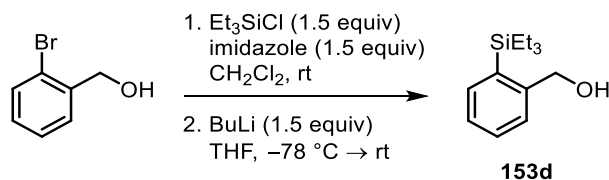
dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 8.0 mL, 20.0 mmol) was added by syringe over approximately 15 minutes, and the solution stirred at this temperature for 30 minutes. Trimethylsilyl chloride (2.8 mL, 27.5 mmol) was then added *via* syringe and the reaction mixture allowed to return to room temperature overnight. The mixture was quenched by the addition of H<sub>2</sub>O (20 mL) and extracted into Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were washed with HCl (0.1 M, 30 mL), then H<sub>2</sub>O (40 mL), dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the resulting oil purified by column chromatography (eluent: 4:1 hexanes/EtOAc) to afford the title compound as a viscous, colourless oil (1.15 g, 30%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 – 7.49 (m, 1H), 7.29 – 7.17 (m, 3H), 2.91 (s, 2H), 1.32 (s, 6H), 0.87 (s, 6H), 0.36 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 145.7, 140.8, 135.3, 131.3, 127.9, 125.2, 76.1, 42.0, 40.9, 26.0, 22.1, 1.8.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3478 (br), 2971 (w), 1469 (w), 1367 (w), 1261 (w), 1247 (m), 1116 (w), 871 (w), 834 (m), 754 (m), 732 (m), 684 (w), 623 (w).

**HRMS:** Calcd. for C<sub>16</sub>H<sub>28</sub>ONaSi: 287.1802 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 287.1805



#### [2-(triethylsilyl)phenyl]methanol (153d)

2-Bromobenzyl alcohol (1.29 g, 6.9 mmol) was added to a flame-dried, N<sub>2</sub>-purged, 100 mL RBF containing a magnetic stirrer bar, and fitted with a rubber septum and inlet needle. CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added *via* syringe, followed by triethylsilyl chloride (1.74 mL, 10.4 mmol) and imidazole (0.70 g, 10.4 mmol). The resulting solution was stirred for 15 hours at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (10 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, 100 mL RBF (again fitted with a septum and inlet needle). THF (20 mL) was added, and the solution cooled to −78 °C in an acetone-dry ice bath. *n*-Butyllithium (1.6 M in hexanes,

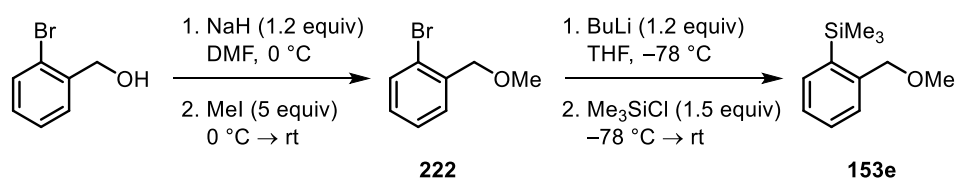
6.5 mL, 10.4 mmol) was added by syringe over approximately 15 minutes, and the solution allowed to return to room temperature overnight. After 14 hours, the mixture was quenched by the addition of H<sub>2</sub>O (10 mL), and extracted into Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the resulting crude oil purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (0.82 g, 53%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.52 – 7.47 (m, 2H), 7.40 (app. td, *J* = 7.5, 1.4 Hz, 1H), 7.28 (app. td, *J* = 7.5, 1.4 Hz, 1H), 4.74 (s, 2H), 0.99 – 0.92 (m, 9H), 0.91 – 0.82 (m, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 146.8, 135.8, 135.1, 129.5, 127.9, 127.0, 65.6, 7.7, 4.5.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3307 (br w), 2952 (m), 2908 (w), 2873 (m), 1456 (w), 1435 (w), 1418 (w), 1235 (w), 1124 (w), 1077 (w), 1002 (m), 713 (m), 672 (m), 606 (w), 582 (w).

**HRMS:** Calcd. for C<sub>13</sub>H<sub>22</sub>OSiNa: 245.1332 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 245.1337



### 1-Bromo-2-(methoxymethyl)benzene (222)

2-Bromobenzyl alcohol (0.94 g, 5.0 mmol) was added to a flame-dried 25 mL RBF equipped with stirrer bar, and purged with N<sub>2</sub> *via* an inlet needle. Anhydrous DMF (7.5 mL) was added *via* syringe and stirring commenced. The temperature was adjusted to 0 °C with an external ice bath, then NaH (60% w/w dispersion in mineral oil, 240 mg, 6.0 mmol) added portion-wise over approximately 15 minutes. Following addition, the reaction mixture was stirred for a further 30 minutes at 0 °C, then methyl iodide (1.57 mL, 25.0 mmol) added in one portion *via* syringe. The reaction mixture was allowed to return to room temperature and stirred for a further 2 hours. The reaction was quenched by addition of a saturated NH<sub>4</sub>Cl solution (10 mL), then extracted into Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were washed with NaOH (3.0 M, 30 mL) then brine (30 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a colourless oil (0.98 g, 97%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.54 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.32 (app. td, *J* = 7.5, 1.3 Hz, 1H), 7.19 – 7.11 (m, 1H), 4.53 (s, 2H), 3.47 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 137.7, 132.7, 129.1, 129.0, 127.5, 122.9, 74.1, 58.7.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2927 (w), 2822 (w), 1470 (w), 1456 (w), 1436 (m), 1379 (w), 1362 (w), 1195 (w), 1120 (m), 1095 (m), 1044 (w), 1026 (m), 974 (w), 943 (w), 924 (w), 748 (s), 668 (w), 633 (w), 605 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>13</sup>

#### **[2-(Methoxymethyl)phenyl]trimethylsilane (153e)**

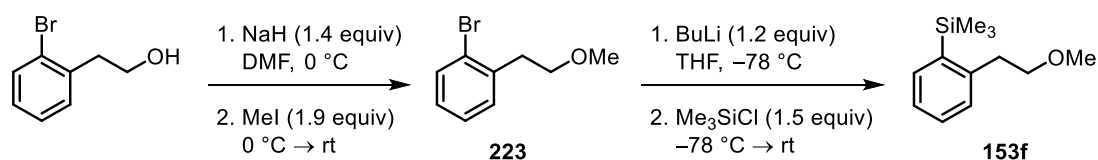
To a nitrogen filled, flame-dried Schlenk flask was added 1-Bromo-2-(methoxymethyl)benzene (0.95 g, 4.7 mmol) along with dry THF (12 mL). The solution was cooled to –78 °C and *n*-butyllithium (2.5 M in hexanes, 2.0 mL, 5.0 mmol) was added dropwise over 15 minutes. The mixture was stirred at –78 °C for a further 30 mins, then trimethylsilylchloride (0.90 mL, 7.0 mmol) added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (10 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (0.37 g, 41%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.55 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.28 (app. td, *J* = 7.3, 1.7 Hz, 1H), 4.54 (s, 2H), 3.41 (s, 3H), 0.34 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.7, 138.7, 134.8, 129.3, 128.5, 127.1, 75.1, 58.1, 0.4.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2953 (w), 2924 (w), 2894 (w), 1456 (w), 1435 (w), 1246 (m), 1192 (w), 1126 (w), 1096 (m), 1075 (w), 834 (s), 746 (m), 726 (m), 686 (w), 622 (w).

**HRMS** calcd. For C<sub>11</sub>H<sub>18</sub>OSiNa: 217.1019 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 217.1011



### 1-Bromo-2-(2-methoxyethyl)benzene (223)

A 250 mL RBF equipped with stirrer bar and rubber septum was flame-dried, then purged with  $\text{N}_2$  through an inlet needle. 2-(2-Bromophenyl)ethanol (5.0 g, 24.9 mmol) was added *via* syringe followed by anhydrous DMF (70 mL), and stirring commenced. The solution was cooled to  $0^\circ\text{C}$  in an ice bath, then NaH (60% w/w dispersion in mineral oil, 1.32 g, 33.0 mmol) was added portion-wise (*Note: A significant amount of  $\text{H}_2$  gas was evolved*). Following addition, the reaction mixture was stirred for 1 hour at  $0^\circ\text{C}$  before methyl iodide (2.8 mL, 45.0 mmol) was added *via* syringe in one portion. The mixture was allowed to return to room temperature overnight. After 11 hours, the reaction was quenched by addition of a saturated  $\text{NH}_4\text{Cl}$  solution (40 mL), then extracted into  $\text{Et}_2\text{O}$  ( $3 \times 40$  mL). The combined organic extracts were washed with NaOH (3.0 M, 30 mL) then brine (30 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 19:1 hexanes/ $\text{EtOAc}$ ) to afford the title compound as a colourless oil (4.95 g, 92%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.51 (dd,  $J = 8.0, 1.2$  Hz, 1H), 7.30 – 7.17 (m, 2H), 7.05 (ddd,  $J = 8.0, 7.0, 2.1$  Hz, 1H), 3.60 (t,  $J = 7.1$  Hz, 2H), 3.35 (s, 3H), 3.02 (t,  $J = 7.1$  Hz, 2H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  138.3, 132.9, 131.2, 128.1, 127.5, 124.8, 71.9, 58.8, 36.5.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2925 (w), 2871 (w), 2823 (w), 1471 (m), 1456 (w), 1438 (w), 1378 (w), 1179 (w), 1110 (m), 1036 (w), 1022 (m), 968 (w), 748 (m), 719 (w), 657 (w).

$^1\text{H}$  and  $^{13}\text{C}$  NMR data are consistent with those reported in the literature.<sup>13</sup>

### [2-(2-Methoxyethyl)phenyl]trimethylsilane (153f)

A 150 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with  $\text{N}_2$  *via* an inlet needle. 2-(2-Bromophenyl)ethyl methyl ether (4.70 g, 21.9 mmol) and THF (60 mL) were added *via* syringe, stirring commenced, and the temperature adjusted to  $-78^\circ\text{C}$  with an external acetone-dry ice bath. *n*-Butyllithium (2.3 M in hexanes, 10.9 mL, 25.0 mmol) was added dropwise over 20 minutes. The solution was stirred for a further 45 minutes at  $-78^\circ\text{C}$ , then trimethylsilyl chloride (3.81 mL, 30.0 mmol) added *via* syringe in one portion. The reaction mixture was allowed to return to room temperature overnight. After 14 hours, the

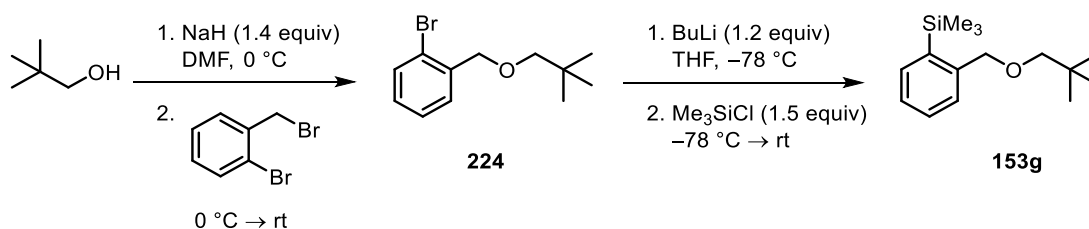
reaction was quenched by addition of H<sub>2</sub>O (50 mL) and extracted into Et<sub>2</sub>O (3 × 50 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated in vacuo, and the residue purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a colourless oil (4.21 g, 92%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.49 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.32 (app. td, *J* = 7.4, 1.5 Hz, 1H), 7.26 – 7.17 (m, 2H), 3.60 – 3.55 (m, 2H), 3.39 (s, 3H), 3.06 – 3.00 (m, 2H), 0.35 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 144.2, 138.9, 134.8, 129.3, 129.2, 125.7, 74.3, 58.9, 36.5, 0.5.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2953 (w), 2925 (w), 2893 (w), 2873 (w), 1472 (w), 1456 (w), 1435 (w), 1248 (m), 1199 (w), 1113 (m), 1080 (w), 968 (w), 834 (s), 753 (m), 727 (m), 688 (w), 622 (w).

**HRMS:** Calcd. for C<sub>12</sub>H<sub>20</sub>OSi: 208.1278 [M]<sup>+</sup>; found (EI<sup>+</sup>): 208.1282



### 1-Bromo-2-[(2,2-dimethylpropoxy)methyl]benzene (224)

A 50 mL RBF equipped with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> through an inlet needle. Neopentyl alcohol (0.35 g, 5.0 mmol) was added followed by anhydrous DMF (15 mL), and stirring commenced. The solution was cooled to 0 °C in an ice bath, then NaH (60% w/w dispersion in mineral oil, 0.40 g, 10.0 mmol) was added portion-wise (*Note: A significant amount of H<sub>2</sub> gas evolved*). Following addition, the reaction mixture was stirred for 2 hours at 0 °C before 2-bromobenzyl bromide (1.36 mL, 10.0 mmol) was added *via* syringe in one portion. The mixture was allowed to return to room temperature overnight. After 14 hours, the reaction was quenched by addition of H<sub>2</sub>O (20 mL), then extracted into Et<sub>2</sub>O (3 × 40 mL). The combined organic extracts were washed with NaOH (3.0 M, 30 mL) then brine (30 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: hexanes) to afford the title compound as a colourless oil (0.75 g, 58%).



**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.52 (m, 2H), 7.32 (app. td, *J* = 7.5, 1.3 Hz, 1H), 7.16 – 7.10 (m, 1H), 4.56 (s, 2H), 3.22 (s, 2H), 0.97 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 138.6, 132.4, 128.7, 128.6, 127.4, 122.3, 81.6, 72.6, 32.4, 27.0.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2953 (w), 2900 (w), 2865 (w), 1472 (w), 1456 (w), 1438 (w), 1384 (w), 1361 (w), 1352 (w), 1220 (w), 1122 (m), 1101 (m), 1044 (w), 1026 (m), 999 (w), 747 (m), 673 (w), 609 (w).

**HRMS:** Calcd. for C<sub>12</sub>H<sub>17</sub>O<sup>79</sup>BrSi: 256.0457 [M]<sup>+</sup>; found (EI<sup>+</sup>): 256.0442

### **{2-[(2,2-Dimethylpropoxy)methyl]phenyl}trimethylsilane (153g)**

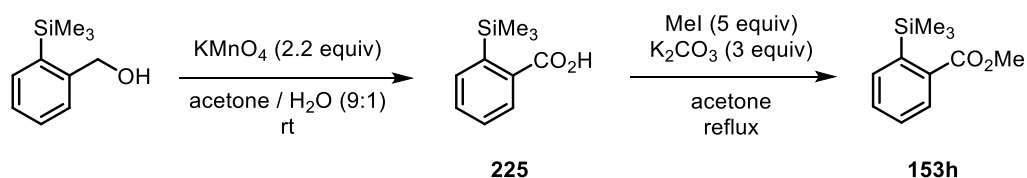
A 50 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> *via* an inlet needle. 1-Bromo-2-[(2,2-dimethylpropoxy)methyl]benzene (0.75 g, 2.9 mmol) and THF (10 mL) were added *via* syringe, stirring commenced, and the temperature adjusted to –78 °C with an external acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 1.3 mL, 3.3 mmol) was added dropwise over 10 minutes. The solution was stirred for a further 15 minutes at –78 °C, then trimethylsilyl chloride (0.51 mL, 4.0 mmol) added *via* syringe in one portion. The reaction mixture was allowed to return to room temperature overnight. After 14 hours, the reaction was quenched by addition of H<sub>2</sub>O (10 mL) and extracted into Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated in vacuo, and the residue purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a colourless oil (0.64 g, 88%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.55 – 7.48 (m, 2H), 7.38 (app. td, *J* = 7.6, 1.5 Hz, 1H), 7.27 (app. td, *J* = 7.3, 1.3 Hz, 1H), 4.60 (s, 2H), 3.17 (s, 2H), 0.96 (s, 9H), 0.34 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 144.6, 137.9, 134.4, 129.3, 127.9, 126.7, 81.4, 73.5, 32.3, 27.1, 0.4.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2953 (w), 2899 (w), 2866 (w), 1473 (w), 1456 (w), 1362 (w), 1248 (m), 1127 (w), 1093 (m), 1076 (m), 1047 (w), 835 (s), 744 (m), 727 (m), 687 (w), 621 (w), 419 (w).

**HRMS:** Calcd. for C<sub>15</sub>H<sub>26</sub>OSi: 250.1748 [M]<sup>+</sup>; found (EI<sup>+</sup>): 250.1754



### 2-(Trimethylsilyl)benzoic acid (225)

2-(Trimethylsilyl)benzyl alcohol (2.20 g, 12.2 mmol), acetone (45 mL), and H<sub>2</sub>O (8 mL) were added to a 150 mL RBF equipped with magnetic stirrer bar, and stirring commenced. KMnO<sub>4</sub> (4.82 g, 30.5 mmol) was added in one portion (*Note: Significant exotherm observed and reaction temperature reached approximately 30 °C*) and the reaction stirred for 3 hours. The reaction mixture was concentrated under reduced pressure then sat. Na<sub>2</sub>SO<sub>3</sub> (20 mL) was added to the residue. The resulting slurry was filtered through a pad of celite (washed copiously with H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>) then transferred to a separating funnel and acidified to pH 4 with HCl (10% w/w). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL) and the combined organic extracts dried over MgSO<sub>4</sub>, and concentrated to a white solid of sufficient purity (2.08 g, 88%).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>):** δ 8.20 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.58 (app. td, *J* = 7.4, 1.3 Hz, 1H), 7.49 (app. td, *J* = 7.7, 1.3 Hz), 0.37 (s, 9H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>):** δ 173.8, 143.9, 135.7, 134.2, 132.4, 131.0, 128.9, 0.4.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2952 (w), 2892 (w), 2657 (w), 2530 (w), 1682 (s), 1561 (m), 1478 (w), 1469 (w), 1411 (m), 1293 (m), 1269 (m), 1260 (m), 1241 (s), 1146 (m), 1117 (m), 917 (w), 840 (s), 807 (m), 753 (w), 730 (s), 682 (m), 652 (m), 621 (m), 555 (m), 482 (m), 422 (w).

**HRMS** calcd. For C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>Si: 217.0655 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 217.0668.

**mp:** 93 – 95 °C (CH<sub>2</sub>Cl<sub>2</sub>); lit. 94 – 95 °C.<sup>16</sup>

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>16</sup>

### Methyl 2-(trimethylsilyl)benzoate (153h)

2-(Trimethylsilyl)benzoic acid (194 mg, 1.0 mmol), K<sub>2</sub>CO<sub>3</sub> (414 mg, 3.0 mmol) and acetone (5mL) were added to a 25 mL RBF fitted with condenser and magnetic stirrer bar. MeI (0.31 mL, 5.0 mmol) was added, stirring commenced, and the reaction mixture heated at reflux for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue suspended between H<sub>2</sub>O (10 mL) and EtOAc (10 mL). The layers

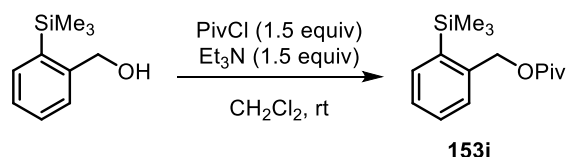
were separated and the aqueous phase extracted with EtOAc ( $3 \times 15$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated in vacuo, and purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (190 mg, 91%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.01 (dd,  $J = 7.7, 1.3$  Hz, 1H), 7.69 (dd,  $J = 7.5, 1.3$  Hz, 1H), 7.50 (app. td,  $J = 7.4, 1.4$  Hz, 1H), 7.43 (app. td,  $J = 7.5, 1.4$  Hz, 1H), 3.91 (s, 3H), 0.32 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  168.9, 142.6, 135.8, 135.6, 131.5, 130.1, 128.9, 52.1, 0.4.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2950 (w), 1722 (s), 1433 (w), 1271 (m), 1252 (m), 1191 (w), 1136 (m), 1111 (m), 1066 (m), 838 (s), 734 (m), 710 (w), 694 (w), 681 (w), 621 (w).

**HRMS** calcd. For  $\text{C}_{11}\text{H}_{17}\text{O}_2\text{Si}$ : 209.0992  $[\text{M}+\text{H}]^+$ ; found (ESI $^+$ ): 209.1022



### [2-(Trimethylsilyl)phenyl]methyl 2,2-dimethylpropanoate (153i)

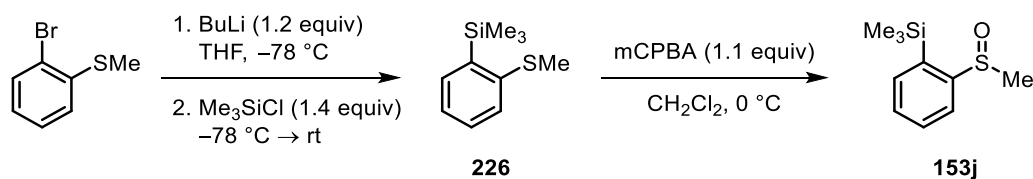
A 25 mL RBF fitted with magnetic stirrer bar and rubber septum was flame-dried and purged with  $\text{N}_2$ . 2-(Trimethylsilyl)benzyl alcohol (180 mg, 1.0 mmol) was added followed by  $\text{CH}_2\text{Cl}_2$  (2.5 mL) and stirring commenced. Pivaloyl chloride (0.18 mL, 1.5 mmol) and triethylamine (0.21 mL, 1.5 mmol) were added *via* syringe. The reaction was stirred overnight, then dry-loaded onto celite and purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (261 mg, 99%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.54 (d,  $J = 7.5$  Hz, 1H), 7.42 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 5.21 (s, 2H), 1.24 (s, 9H), 0.36 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  178.4, 141.7, 139.1, 134.7, 129.5, 128.8, 127.5, 66.4, 39.0, 27.4, 0.4.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2958 (w), 2904 (w), 1727 (m), 1479 (w), 1461 (w), 1396 (w), 1279 (m), 1263 (w), 1250 (m), 1206 (w), 1141 (m), 1078 (w), 1032 (w), 963 (w), 942 (w), 836 (s), 756 (m), 744 (m), 727 (m), 689 (w), 622 (w).

**HRMS** calcd. For  $\text{C}_{15}\text{H}_{25}\text{O}_2\text{Si}$ : 265.1618  $[\text{M}+\text{H}]^+$ ; found (ESI $^+$ ): 265.1612.



### Trimethyl[2-(methylsulfanyl)phenyl]silane (226)

A 150 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> *via* an inlet needle. 1-Bromo-2-(methylsulfanyl)benzene (5.0 g, 24.6 mmol) and THF (75 mL) were added *via* syringe, stirring commenced, and the temperature adjusted to  $-78^\circ\text{C}$  with an external acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 12.0 mL, 30.0 mmol) was added dropwise over 20 minutes. The solution was stirred for a further 45 minutes at  $-78^\circ\text{C}$ , then trimethylsilyl chloride (4.44 mL, 35.0 mmol) added *via* syringe in one portion. The reaction mixture was allowed to return to room temperature overnight. After 12 hours, the reaction was quenched by addition of H<sub>2</sub>O (50 mL) and extracted into Et<sub>2</sub>O (3  $\times$  50 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the residue purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a colourless oil (4.59 g, 95%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.48 – 7.41 (m, 1H), 7.38 – 7.22 (m, 2H), 7.16 (ddd,  $J = 7.3, 5.7, 2.7$  Hz, 1H), 2.49 (s, 3H), 0.39 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  145.0, 140.3, 134.8, 129.9, 127.7, 125.0, 18.1, 0.0.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 2952 (w), 2920 (w), 1574 (w), 1557 (w), 1421 (m), 1246 (m), 1126 (w), 1107 (w), 1048 (w), 966 (w), 835 (s), 743 (m), 715 (m), 689 (w), 659 (w), 620 (w), 454 (w), 436 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>17</sup>

### (2-Methanesulfinylphenyl)trimethylsilane (153j)

A 100 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> *via* an inlet needle. Trimethyl[2-(methylsulfanyl)phenyl]silane (1.96 g, 10.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added *via* syringe and the stirred solution cooled to  $0^\circ\text{C}$ . meta-Chloroperoxybenzoic acid (mCPBA, ~77% w/w, 2.47 g, 11.0 mmol) was added

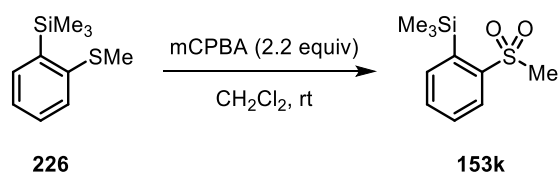
portion-wise over approximately 15 minutes, then the reaction mixture allowed to return to room temperature and stirred for a further 3 hours. The reaction was quenched by addition of sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (25 mL) and extracted into EtOAc (3 × 30 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by column chromatography (eluent 1:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (1.72 g, 81%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.13 (ddd, *J* = 7.9, 1.2, 0.6 Hz, 1H), 7.62 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1H), 7.55 (ddd, *J* = 7.4, 1.5, 0.5 Hz, 1H), 7.47 (app. td, *J* = 7.4, 1.2 Hz, 1H), 2.68 (s, 3H), 0.38 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 152.7, 138.0, 134.7, 131.0, 130.8, 123.4, 44.4, 0.9.

**v<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2954 (w), 1456 (w), 1417 (w), 1249 (m), 1106 (w), 1060 (m), 1033 (m), 950 (w), 836 (s), 754 (m), 716 (m), 690 (w), 676 (w), 658 (w), 621 (w), 495 (w), 451 (w).

**HRMS** calcd. For C<sub>10</sub>H<sub>16</sub>OSSi: 212.0686 [M]<sup>+</sup>; found (EI<sup>+</sup>): 212.0676



### (2-Methanesulfonylphenyl)trimethylsilane (153k)

A 100 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> *via* an inlet needle. Trimethyl[2-(methylsulfanyl)phenyl]silane (1.96 g, 10.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added *via* syringe and stirring commenced. meta-Chloroperoxybenzoic acid (mCPBA, ~77% w/w, 2.47 g, 11.0 mmol) was added portion-wise over approximately 15 minutes and stirred for a further 5 hours at room temperature. The reaction was quenched by addition of sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (25 mL) and extracted into EtOAc (3 × 30 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by column chromatography (eluent 3:1 hexanes/EtOAc) to afford the title compound as a white solid. Recrystallisation from CH<sub>2</sub>Cl<sub>2</sub> afforded fine white crystals (1.67 g, 73%).

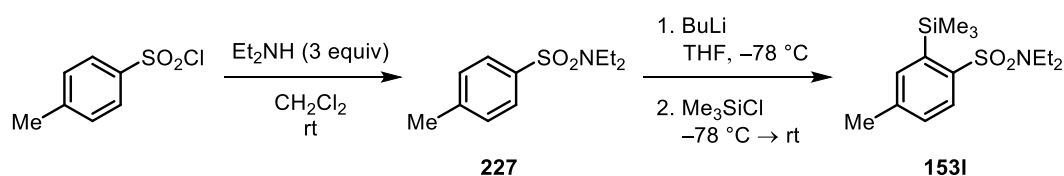
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.09 – 8.02 (m, 1H), 7.83 – 7.79 (m, 1H), 7.64 – 7.53 (m, 2H), 3.01 (s, 3H), 0.44 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 146.0, 140.5, 136.9, 132.7, 130.0, 129.5, 45.2, 1.3.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2949 (w), 2897 (w), 1455 (w), 1416 (w), 1300 (m), 1281 (m), 1240 (m), 1165 (w), 1145 (m), 1120 (m), 1102 (m), 1046 (w), 951 (m), 836 (s), 782 (m), 745 (s), 723 (m), 711 (m), 681 (m), 657 (m), 621 (m), 543 (s), 529 (s), 475 (m), 453 (m), 430 (w).

**HRMS** calcd. For C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>SSiNa: 251.0532 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 251.0534

**mp:** 80 – 82 °C (CH<sub>2</sub>Cl<sub>2</sub>)



#### ***N,N*-Diethyl-4-methylbenzenesulfonamide (**227**)**

A 100 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> through an inlet needle. *p*-Toluenesulfonyl chloride (5.0 g, 26.2 mmol) was added, followed by dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL), and stirring commenced. The mixture was cooled to 0 °C in an ice bath, then diethylamine (8.1 mL, 78.6 mmol) added dropwise over 15 minutes. The cold bath was removed and the reaction mixture stirred at room temperature for 14 hours. A saturated solution of NH<sub>4</sub>Cl (25 mL) was added and the aqueous phase extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and recrystallised from hot EtOH to produce the title compound as white crystalline needles (4.57 g, 77%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.70 (m, 2H), 7.32 – 7.27 (m, 2H), 3.23 (q, *J* = 7.1 Hz, 4H), 2.42 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.0, 137.5, 129.7, 127.1, 42.1, 21.6, 14.3.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2991 (w), 2974 (w), 2935 (w), 1597 (w), 1493 (w), 1465 (w), 1456 (w), 1374 (w), 1354 (w), 1329 (m), 1305 (w), 1291 (w), 1199 (m), 1171 (w), 1154 (s), 1087 (m), 1071 (w), 1040 (w), 1012 (m), 927 (m), 814 (m), 797 (w), 777 (m), 711 (m), 696 (m), 642 (m), 558 (m), 543 (s), 430 (w).

**mp:** 61 – 64 °C (EtOH); lit. 58 – 59 °C.<sup>18</sup>

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>18</sup>

***N,N*-Diethyl-4-methyl-2-(trimethylsilyl)benzenesulfonamide (153l)**

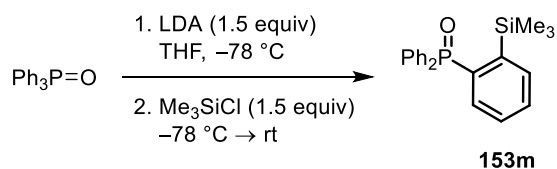
A 100 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> through an inlet needle. *N,N*-Diethyl-4-methylbenzenesulfonamide (1.14 g, 5.0 mmol) was added, followed by dry THF (50 mL) and stirring commenced. The reaction mixture was cooled to –78 °C in an acetone-dry ice bath then *n*-butyllithium (2.5 M, 2.4 mL, 6.0 mmol) added dropwise *via* syringe over 10 minutes. The solution was stirred at –78 °C for 45 minutes then trimethylsilyl chloride (1.01 mL, 8.0 mmol) added in one portion. The reaction mixture was allowed to return to room temperature overnight. After 12 hours, the reaction was quenched by the addition of H<sub>2</sub>O (40 mL) and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and purified by column chromatography (eluent: 1:1 CH<sub>2</sub>Cl<sub>2</sub>/hexanes) to afford the title compound as a colourless oil (1.26 g, 84%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.62 – 7.54 (m, 2H), 7.29 – 7.25 (m, 1H), 3.33 (q, *J* = 7.1 Hz, 4H), 2.42 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 6H), 0.43 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.6, 141.4, 140.4, 137.3, 130.0, 127.2, 42.0, 21.7, 14.5, 1.3.

***v*<sub>max</sub>(neat)/cm<sup>–1</sup>:** 2977 (w), 2950 (w), 2926 (w), 2894 (w), 1456 (w), 1446 (w), 1417 (w), 1380 (w), 1248 (m), 1130 (w), 1091 (m), 1056 (w), 926 (w), 837 (s), 790 (m), 761 (m), 724 (m), 680 (w), 643 (w), 622 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>19</sup>



### [2-(Diphenylphosphoroso)phenyl]trimethylsilane (153m)

A 250 mL RBF equipped with magnetic stirrer and rubber septum was flame-dried, then purged under a stream of  $\text{N}_2$  through an inlet needle. Triphenylphosphine oxide (2.78 g, 10.0 mmol) was added followed by THF (90 mL) and stirring commenced. The temperature was adjusted to  $-78\text{ }^\circ\text{C}$  with an acetone-dry ice bath and LDA (2.0 M in THF, 7.5 mL, 15.0 mmol) added dropwise over 15 minutes. The resulting mixture was stirred for 1 hour at  $-78\text{ }^\circ\text{C}$ , then trimethylsilyl chloride (1.9 mL, 15.0 mmol) added in one portion. The stirred solution was allowed to return to room temperature overnight. After 16 hours the reaction was quenched by the addition of  $\text{H}_2\text{O}$  (50 mL), then extracted into EtOAc ( $3 \times 50\text{ mL}$ ), and the combined organic extracts dried over  $\text{MgSO}_4$  then concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 65:35 hexanes/EtOAc) to afford the title compound as a white solid (2.29 g, 65%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.89 – 7.83 (m, 1H), 7.60 – 7.39 (m, 11H), 7.29 (app. tdd,  $J = 7.5, 2.9, 1.3\text{ Hz}$ , 1H), 7.18 (dddd,  $J = 13.8, 7.7, 1.3, 0.6\text{ Hz}$ , 1H), 0.33 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  146.6 (d,  $J = 15.2\text{ Hz}$ ), 137.1 (d,  $J = 106.0\text{ Hz}$ ), 136.6 (d,  $J = 15.0\text{ Hz}$ ), 134.5 (d,  $J = 100.7\text{ Hz}$ ), 133.5 (d,  $J = 15.7\text{ Hz}$ ), 132.2 (d,  $J = 9.7\text{ Hz}$ ), 131.5 (d,  $J = 2.9\text{ Hz}$ ), 130.5 (d,  $J = 2.9\text{ Hz}$ ), 128.3 (d,  $J = 12.2\text{ Hz}$ ), 127.6 (d,  $J = 13.3\text{ Hz}$ ), 1.6 (s).

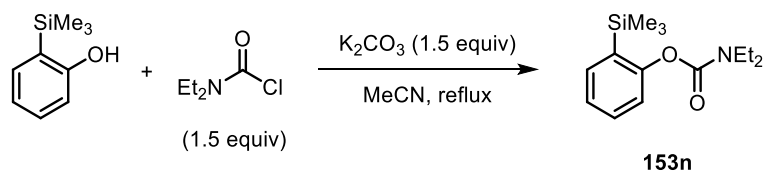
**$^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ):**  $\delta$  32.3

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 3430 (w), 2945 (w), 1435 (m), 1242 (m), 1179 (m), 1116 (m), 1100 (m), 1054 (w), 842 (s), 750 (m), 727 (s), 695 (m), 660 (m), 623 (w), 540 (s), 504 (m), 473 (m), 456 (m), 441 (w).

**HRMS:** Calcd. for  $\text{C}_{21}\text{H}_{24}\text{OPSi}$ : 351.1329  $[\text{M}+\text{H}]^+$ ; found (ESI $^+$ ): 351.1333

**mp:** 98 – 102  $^\circ\text{C}$  (EtOAc)





### 2-(Trimethylsilyl)phenyl *N,N*-diethylcarbamate (**153n**)

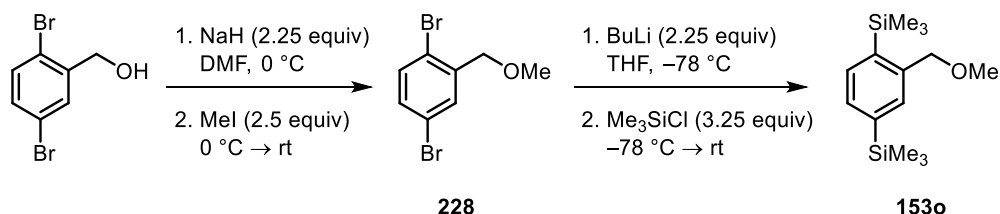
2-(Trimethylsilyl)phenol (1.11 g, 6.7 mmol), K<sub>2</sub>CO<sub>3</sub> (1.38 g, 10.0 mmol) and MeCN (13.5 mL) were added to a 50 mL RBF containing a magnetic stirrer bar and stirring commenced. Diethylcarbamoyl chloride (1.26 mL, 10.0 mmol) was added, then a condenser fitted to the flask and the reaction mixture heated at reflux for 3.5 hours. Once the reaction had cooled to room temperature, H<sub>2</sub>O (10 mL) was added, and the aqueous layer extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 100:0 → 80:20 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (0.89 g, 49%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.46 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.37 (ddd, *J* = 8.1, 7.3, 1.8 Hz, 1H), 7.18 (app. td, *J* = 7.4, 1.1 Hz, 1H), 7.04 (dd, *J* = 8.1, 1.0 Hz, 1H), 3.49 (q, *J* = 7.1 Hz, 2H), 3.40 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.28 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 156.5, 154.6, 135.0, 131.7, 130.5, 124.9, 122.4, 42.1, 41.7, 14.4, 13.5, −0.7.

**ν<sub>max</sub>(neat)/cm<sup>−1</sup>:** 2971 (w), 1714 (s), 1593 (w), 1541 (w), 1507 (w), 1468 (w), 1457 (w), 1411 (m), 1379 (w), 1350 (w), 1315 (w), 1273 (m), 1257 (m), 1225 (w), 1187 (s), 1151 (s), 1125 (m), 1098 (w), 1077 (m), 1042 (w), 960 (w), 937 (w), 836 (s), 786 (w), 747 (m), 715 (m), 691 (w), 620 (w), 451 (w).

**HRMS** calcd. For C<sub>14</sub>H<sub>24</sub>O<sub>2</sub>NSi: 266.1571 [M+H]<sup>+</sup>; found (ESI<sup>+</sup>): 266.1580



### 1,4-Dibromo-2-(methoxymethyl)benzene (228)

A 150 mL RBF equipped with stirrer bar and rubber septum was flame-dried, then purged with  $\text{N}_2$  through an inlet needle. (2,5-Dibromophenyl)methanol (5.0 g, 18.8 mmol) was added followed by anhydrous DMF (60 mL), and stirring commenced. The solution was cooled to  $0^\circ\text{C}$  in an ice bath, then NaH (60% w/w dispersion in mineral oil, 1.60 g, 40.0 mmol) was added portion-wise. Following addition, the reaction mixture was stirred for 45 minutes at  $0^\circ\text{C}$ , then methyl iodide (2.8 mL, 45.0 mmol) added *via* syringe in one portion. The mixture was allowed to return to room temperature and stirred for a further 3 hours. The reaction was quenched by addition of  $\text{H}_2\text{O}$  (10 mL), then extracted into  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic extracts were washed with NaOH (3.0 M, 30 mL) then brine (30 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to afford the title compound as a clear, colourless oil without the need for additional purification (5.10 g, 97%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.62 (m, 1H), 7.38 (d,  $J = 8.4$  Hz, 1H), 7.29 – 7.24 (m, 1H), 4.47 (s, 2H), 3.48 (s, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  139.9, 133.9, 131.9, 131.7, 121.7, 120.9, 73.4, 58.9.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2922 (w), 2852 (w), 2819 (w), 1557 (w), 1540 (w), 1456 (m), 1387 (w), 1375 (m), 1254 (w), 1198 (m), 1109 (m), 1082 (m), 1057 (w), 1024 (m), 975 (w), 928 (w), 882 (w), 865 (w), 806 (m), 528 (w), 434 (w), 419 (w).

**HRMS:** Calcd. for  $\text{C}_8\text{H}_8\text{O}^{79}\text{Br}_2$ : 277.8936  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 277.8944

### [3-(Methoxymethyl)-4-(trimethylsilyl)phenyl]trimethylsilane (153o)

A 150 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with  $\text{N}_2$  *via* an inlet needle. 1,4-Dibromo-2-(methoxymethyl)benzene (5.10 g, 18.2 mmol) and THF (50 mL) were added *via* syringe, stirring commenced, and the temperature adjusted to  $-78^\circ\text{C}$  with an external acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 18.0 mL, 45.0 mmol) was added dropwise over 30 minutes. The solution was stirred for a further 45 minutes at  $-78^\circ\text{C}$ , then trimethylsilyl chloride (7.6 mL, 60.0 mmol) added *via* syringe in one portion.

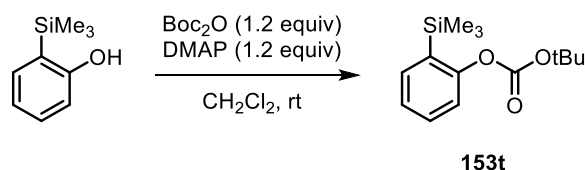
The reaction mixture was allowed to return to room temperature overnight. The reaction was quenched by addition of H<sub>2</sub>O (30 mL) and extracted into Et<sub>2</sub>O (3 × 40 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated in vacuo, and the residue purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil that crystallised to a waxy solid on standing (1.70 g, 35%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 – 7.52 (m, 2H), 7.47 – 7.43 (dd, *J* = 7.1, 1.3 Hz, 1H), 4.54 (s, 2H), 3.42 (s, 3H), 0.34 (s, 9H), 0.28 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 142.6, 141.6, 139.4, 134.2, 133.5, 132.2, 75.4, 58.2, 0.4, -1.0.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2955 (w), 2928 (w), 2896 (w), 1456 (w), 1378 (w), 1244 (m), 1199 (m), 1144 (m), 1121 (m), 1107 (m), 978 (w), 902 (w), 831 (s), 813 (s), 747 (s), 688 (m), 637 (m), 619 (m), 543 (w), 480 (w), 428 (m),

**HRMS:** Calcd. for C<sub>14</sub>H<sub>26</sub>OSi<sub>2</sub>: 266.1517 [M]<sup>+</sup>; found (EI<sup>+</sup>): 266.1513



### Tert-butyl 2-(trimethylsilyl)phenyl carbonate (153t)

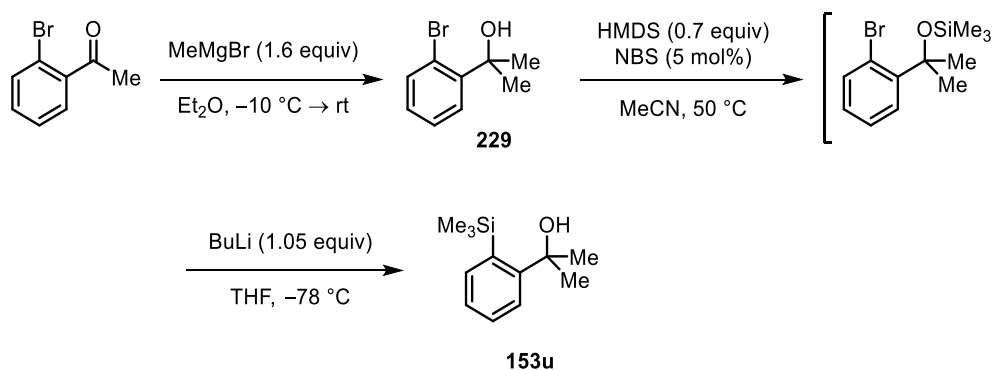
2-(Trimethylsilyl)phenol (1.66 g, 10.0 mmol) was added to a 100 mL RBF equipped with stirrer bar, followed by CH<sub>2</sub>Cl<sub>2</sub> (30 mL), di-*tert*-butyldicarbonate (2.62 g, 12.0 mmol), and dimethylaminopyridine (DMAP, 1.47 g, 12.0 mmol). The reaction mixture was stirred at room temperature overnight, then dry-loaded onto silica and purified by column chromatography (eluent: 100:0 → 80:20 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (1.65 g, 62%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.46 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.39 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H), 7.21 (app. td, *J* = 7.4, 1.1 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.0 Hz, 1H), 1.55 (s, 9H), 0.30 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.9, 152.4, 135.1, 131.8, 130.5, 125.6, 122.0, 83.2, 27.9, -0.8.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 2979 (w), 1755 (s), 1717 (w), 1595 (w), 1541 (w), 1507 (w), 1472 (w), 1457 (w), 1436 (w), 1395 (w), 1369 (w), 1273 (m), 1246 (s), 1202 (w), 1141 (s), 1081 (m), 1048 (w), 1015 (w), 892 (w), 838 (m), 783 (m), 753 (m), 732 (m), 710 (w), 693 (w), 676 (w), 621 (w), 603 (w), 453(w).

**HRMS:** Calcd. for  $\text{C}_{14}\text{H}_{22}\text{O}_3\text{NaSi}$ : 289.1230  $[\text{M}+\text{Na}]^+$ ; found (ESI<sup>+</sup>): 289.1234



### 2-(2-Bromophenyl)propan-2-ol (229)

A 250 mL RBF equipped with magnetic stirrer bar and rubber septum was flame-dried then purged with  $\text{N}_2$  via an inlet needle. 2-Bromoacetophenone (4.0 mL, 29.8 mmol) was added by syringe followed by dry  $\text{Et}_2\text{O}$  (300 mL), and stirring commenced. The solution was cooled to  $-10\text{ }^\circ\text{C}$  in an ice-salt bath, then  $\text{MeMgBr}$  (3.0 M in  $\text{Et}_2\text{O}$ , 15.9 mL, 47.7 mmol) added dropwise over 30 minutes. The reaction was allowed to return to room temperature overnight, then poured onto ice (100 g) and sat.  $\text{NH}_4\text{Cl}$  (100 mL) added. The mixture was transferred to a separating funnel and the aqueous phase extracted with additional  $\text{Et}_2\text{O}$  (3 x 200 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated under reduced pressure, and the residue purified by column chromatography (eluent: 100:0  $\rightarrow$  80:20 hexanes/ $\text{EtOAc}$ ) to afford the title compound as a clear, colourless oil (1.15 g, 18%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.67 (dd,  $J = 7.9, 1.7$  Hz, 1H), 7.58 (dd,  $J = 7.9, 1.4$  Hz, 1H), 7.30 (ddd,  $J = 7.9, 7.3, 1.4$  Hz, 1H), 7.10 (ddd,  $J = 7.9, 7.3, 1.7$  Hz, 1H), 1.76 (s, 6H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  146.2, 135.2, 128.7, 127.7, 127.4, 120.6, 73.7, 29.7.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3402 (br w), 2971 (w), 2929 (w), 1463 (w), 1424 (w), 1363 (w), 1336 (w), 1266 (w), 1230 (w), 1170 (m), 1138 (w), 1097 (w), 1047 (w), 1017 (m), 951 (m), 856 (w), 754 (m), 724 (m), 651 (w), 564 (w).

$^1\text{H}$  and  $^{13}\text{C}$  NMR data are consistent with those reported in the literature.<sup>20</sup>

## 2-[2-(Trimethylsilyl)phenyl]propan-2-ol (153u)

*Note: The NBS catalysed silylation reaction was based on a literature procedure.<sup>9</sup>*

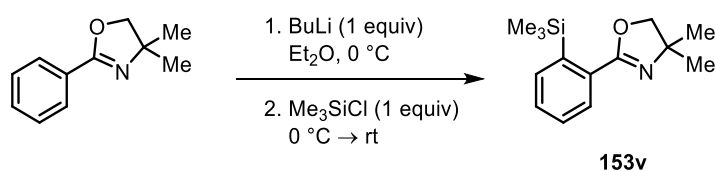
2-(2-Bromophenyl)propan-2-ol (1.12 g, 5.2 mmol) was added to a flame-dried, N<sub>2</sub>-purged, 100 mL RBF containing a magnetic stirrer bar, and fitted with a rubber septum and inlet needle. MeCN (15 mL) was added *via* syringe, followed by hexamethyldisilazane (HMDS, 0.77 mL, 3.7 mmol). The resulting solution was stirred for 15 mins at room temperature, then *N*-bromosuccinimide (NBS, 46 mg, 0.25 mmol) added in one portion. The temperature was adjusted to 50 °C and stirring maintained for a further 2 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (5 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, 100 mL RBF (again fitted with a septum and inlet needle). THF (15 mL) was added, and the solution cooled to –78 °C in an acetone-dry ice bath. BuLi (2.3 M in hexane, 2.4 mL, 5.5 mmol) was added by syringe over approximately 15 minutes, and the solution allowed to return to room temperature overnight. After 16 hours, the mixture was quenched by the addition of H<sub>2</sub>O (10 mL), and extracted into Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the resulting crude oil purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (0.65 g, 60%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.74 – 7.65 (m, 1H), 7.37 – 7.29 (m, 1H), 7.26 – 7.17 (m, 2H), 1.64 (s, 1H), 1.61 (s, 6H), 0.34 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 155.0, 136.4, 136.0, 128.9, 125.9, 125.2, 75.0, 33.4, 3.5.

***v*<sub>max</sub>(neat)/cm<sup>–1</sup>:** 2948 (w), 2898 (w), 1362 (w), 1243 (m), 1180 (w), 1115 (m), 1099 (w), 1064 (w), 958 (w), 836 (m), 764 (m), 731 (m), 667 (m), 622 (w), 561 (w), 470 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>21</sup>



**4,4-Dimethyl-2-[2-(trimethylsilyl)phenyl]-4,5-dihydro-1,3-oxazole (153v)**

*Prepared according to the following modified literature procedure:<sup>22</sup>*

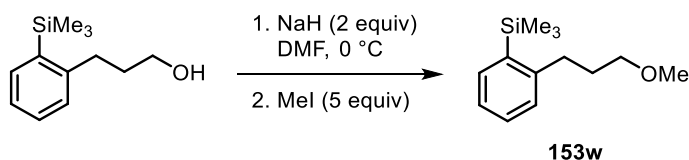
A Schlenk tube equipped with magnetic stirrer bar was flame-dried, then evacuated and backfilled with N<sub>2</sub> three times. 4,4-Dimethyl-2-phenyl-4,5-dihydrooxazole (1.05 g, 6 mmol) and Et<sub>2</sub>O (6 mL) were added sequentially *via* syringe and stirring commenced. The temperature was adjusted to 0 °C in an ice-water bath, then *n*-butyllithium (2.5 M in hexanes, 2.4 mL, 6.0 mmol) added dropwise over approximately 10 mins. The reaction mixture was stirred at 0 °C for 1 hour, then trimethylsilyl chloride (0.76 mL, 6.0 mmol) added dropwise *via* syringe. The resulting solution was allowed to return to room temperature overnight. After 14 hours, the reaction mixture was quenched by addition of H<sub>2</sub>O (10 mL). Additional Et<sub>2</sub>O (10 mL) was added, the layers separated, and the aqueous phase further extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: 100:0 → 80:20 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (1.05 g, 71%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.91 – 7.87 (m, 1H), 7.65 – 7.60 (m, 1H), 7.39 (app. pd, *J* = 7.4, 1.6 Hz, 2H), 4.10 (s, 2H), 1.39 (s, 6H), 0.32 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 163.6, 140.2, 135.2, 133.8, 129.7, 129.5, 128.7, 79.1, 67.8, 28.5, 0.7.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2964 (w), 2892 (w), 1653 (m), 1457 (w), 1363 (w), 1349 (w), 1307 (w), 1242 (m), 1188 (w), 1128 (w), 1092 (m), 1057 (w), 1038 (m), 991 (w), 967 (w), 837 (s), 779 (w), 750 (w), 729 (m), 688 (m), 656 (m), 618 (w), 470 (w).

**HRMS** calcd. For C<sub>14</sub>H<sub>21</sub>ONSi: 247.1387 [M]<sup>+</sup>; found (EI<sup>+</sup>): 247.1398



### [2-(3-Methoxypropyl)phenyl]trimethylsilane (**153w**)

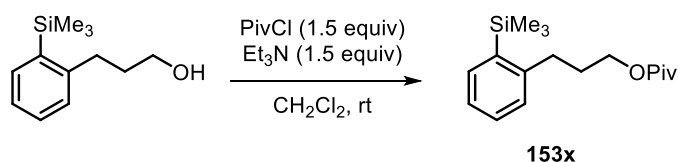
A 25 mL RBF equipped with magnetic stirrer bar and rubber septum was flame-dried, then purged with a stream of N<sub>2</sub> through an inlet needle. 3-[2-(Trimethylsilyl)phenyl]propan-1-ol (1.11 g, 5.4 mmol) and DMF (7.5 mL) were added and stirring commenced. The temperature was adjusted to 0 °C with an ice-water bath, then NaH (60% w/w dispersion in mineral oil, 0.40 g, 10.0 mmol) was added portionwise with concurrent evolution of H<sub>2</sub> gas. The reaction mixture was stirred at 0 °C for 45 mins, then methyl iodide (1.67 mL, 26.7 mmol) added in one portion and the reaction allowed to return to room temperature. After 14 hours, the reaction was cooled to 0 °C and carefully quenched by the slow addition of MeOH (2 mL) then H<sub>2</sub>O (10 mL). Et<sub>2</sub>O (20 mL) was added, the layers separated, and the aqueous phase extracted with additional Et<sub>2</sub>O (3 × 15 mL). The combined organic extracts were washed with H<sub>2</sub>O (20 mL) then brine (2 × 20 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure (*Note: ~2 mL Et<sub>3</sub>N was added to the distillate to quench any remaining methyl iodide*). The residue was purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (0.91 g, 77%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.51 – 7.45 (m, 1H), 7.35 – 7.28 (m, 1H), 7.25 – 7.15 (m, 2H), 3.46 (app. td, *J* = 6.4, 1.0 Hz, 2H), 3.37 (d, *J* = 1.0 Hz, 3H), 2.84 – 2.75 (m, 2H), 1.95 – 1.85 (m, 2H), 0.34 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 148.0, 138.3, 134.7, 129.4, 128.7, 125.3, 72.6, 58.8, 32.8, 32.4, 0.6.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2952 (w), 2894 (w), 2869 (w), 1472 (w), 1456 (w), 1435 (w), 1385 (w), 1261 (w), 1248 (m), 1117 (m), 1084 (w), 834 (s), 752 (m), 727 (m), 687 (w), 622 (w), 455 (w), 419 (w).

**HRMS** calcd. For C<sub>13</sub>H<sub>22</sub>OSi: 222.1435 [M]<sup>+</sup>; found (EI<sup>+</sup>): 222.1413



### 3-[2-(Trimethylsilyl)phenyl]propyl 2,2-dimethylpropanoate (153x)

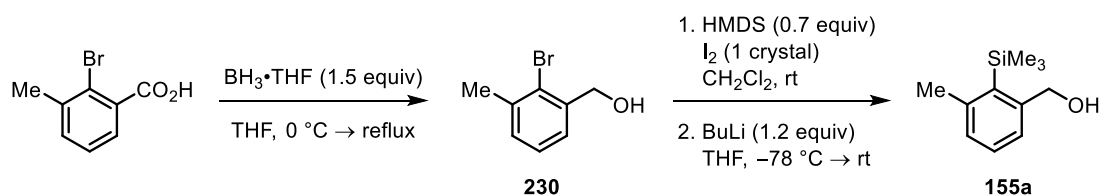
A 25 mL RBF fitted with magnetic stirrer bar and rubber septum was flame-dried and purged with N<sub>2</sub>. 3-[2-(Trimethylsilyl)phenyl]propan-1-ol (208 mg, 1.0 mmol) was added followed by CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) and stirring commenced. PivCl (0.18 mL, 1.5 mmol) and Et<sub>3</sub>N (0.21 mL, 1.5 mmol) were added *via* syringe. The reaction was stirred overnight, then dry-loaded onto celite and purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (273 mg, 93%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.48 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.32 (app. td, *J* = 7.5, 1.5 Hz, 1H), 7.23 – 7.12 (m, 2H), 4.16 (t, *J* = 6.5 Hz), 2.81 (m, 2H), 1.96 (m, 2H), 1.22 (s, 9H), 0.34 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 178.8, 147.3, 138.3, 134.8, 129.5, 128.7, 125.5, 64.5, 39.0, 32.9, 31.5, 27.4, 0.6.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2956 (w), 1727 (m), 1282 (m), 1262 (w), 1249 (m), 1149 (m), 1127 (w), 1087 (w), 835 (m), 753 (m), 727 (m), 688 (w), 622 (w).

**HRMS** calcd. For C<sub>16</sub>H<sub>27</sub>O<sub>2</sub>Si: 293.1931 [M+H]<sup>+</sup>; found (ESI<sup>+</sup>): 293.1919.



### (2-Bromo-3-methylphenyl)methanol (230)

2-Bromo-3-methylbenzoic acid (10.0 g, 46.5 mmol) was added to a 1 L round-bottomed flask followed by dry THF (200 mL) and stirring commenced. The temperature was adjusted to 0 °C, then BH<sub>3</sub>·THF (1.0 M in THF, 70 mL, 70 mmol) was added dropwise (*Note: significant amount of H<sub>2</sub> gas evolved*). The solution was allowed to stir at room temperature overnight. H<sub>2</sub>O (approx. 10 mL) was added cautiously, and after the gas evolution had ceased, sat. Na<sub>2</sub>CO<sub>3</sub> (100 mL) was added and the reaction mixture extracted into EtOAc (3 × 100 mL).



The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated in vacuo to yield a pale yellow solid. Recrystallisation from refluxing hexane afforded the title compound as a white crystalline solid (5.88 g, 63%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.28 (m, 1H), 7.25 – 7.15 (m, 2H), 4.75 (s, 2H), 2.42 (s, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  140.2, 138.6, 130.2, 127.3, 126.4, 125.3, 65.8, 23.5.

**$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ :** 3248 (m, br), 2917 (w), 2856 (w), 1452 (m), 1407 (m), 1372 (m), 1349 (m), 1240 (m), 1168 (w), 1056 (s), 1025 (m), 988 (m), 900 (w), 769 (m), 759 (m), 695 (w), 644 (m), 618 (m, br), 531 (w).

**HRMS** calcd. For  $\text{C}_8\text{H}_9\text{O}^{79}\text{Br}$ : 199.9831  $[\text{M}]^+$ ; found (EI $^+$ ): 199.9838

**mp:** 88 – 91 °C (hexane)

### [3-Methyl-2-(trimethylsilyl)phenyl]methanol (155a)

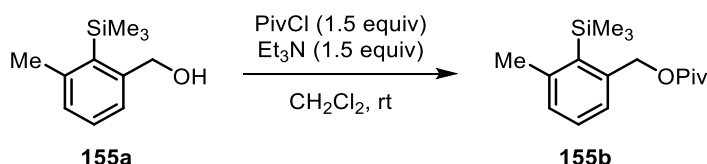
A 50 mL RBF equipped with stirrer bar and rubber septum was flame-dried then purged with  $\text{N}_2$  through an inlet needle. (2-Bromo-3-methylphenyl)methanol (1.00 g, 5.0 mmol),  $\text{CH}_2\text{Cl}_2$  (10 mL), and hexamethyldisilazane (HMDS, 0.73 mL, 3.5 mmol) were added *via* syringe (in that order) and stirring commenced. A single crystal of iodine was added, then stirring was maintained at room temperature for 15 minutes. Solid  $\text{Na}_2\text{S}_2\text{O}_3$  (approx. 3 g) was added and the reaction mixture stirred for a further 30 minutes, then passed through a short pad of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried,  $\text{N}_2$ -purged, round-bottomed flask (again fitted with rubber septum and inlet needle). THF (20 mL) was added, and the solution cooled to  $-78^\circ\text{C}$  in an acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 2.4 mL, 6.0 mmol) was added by syringe over approximately 15 minutes, and the solution allowed to return to room temperature overnight. The mixture was quenched by the addition of  $\text{H}_2\text{O}$  (10 mL) and extracted into EtOAc ( $3 \times 20$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated *in vacuo*, and the resulting oil purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (0.75 g, 77%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.30 – 7.24 (m, 2H), 7.15 – 7.08 (m, 1H), 4.76 (s, 2H), 2.51 (s, 3H), 0.45 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  147.0, 144.8, 137.2, 130.4, 129.2, 126.4, 66.2, 24.8, 3.4.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3307 (w, br), 2952 (w), 2897 (w), 1557 (w), 1540 (w), 1520 (w), 1507 (w), 1472 (w), 1456 (w), 1445 (w), 1417 (w), 1377 (w), 1249 (m), 1129 (w), 1056 (w), 1018 (w), 835 (s), 792 (m), 760 (m), 725 (m), 679 (w), 642 (w), 619 (w).

**HRMS** calcd. For  $\text{C}_{11}\text{H}_{18}\text{OSi}$ : 194.1122  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 194.1129



### [3-Methyl-2-(trimethylsilyl)phenyl]methyl 2,2-dimethylpropanoate (155b)

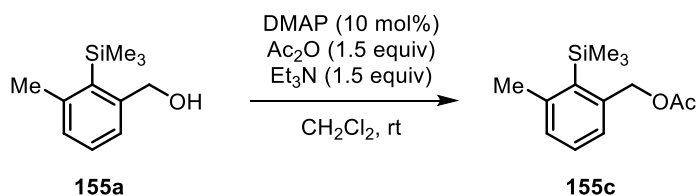
A 25 mL RBF fitted with magnetic stirrer bar and rubber septum was flame-dried and purged with  $\text{N}_2$ . [3-Methyl-2-(trimethylsilyl)phenyl]methanol (388 mg, 2.0 mmol) was added followed by  $\text{CH}_2\text{Cl}_2$  (5 mL) and stirring commenced. PivCl (0.36 mL, 3.0 mmol) and  $\text{Et}_3\text{N}$  (0.42 mL, 3.0 mmol) were added *via* syringe. The reaction was stirred overnight, then dry-loaded onto celite and purified by column chromatography (eluent: 19:1 hexanes/ $\text{EtOAc}$ ) to afford the title compound as a clear, colourless oil (362 mg, 65%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.28 – 7.17 (m, 2H), 7.12 (dd,  $J = 7.4, 1.6$  Hz, 1H), 5.17 (s, 2H), 2.50 (s, 3H), 1.22 (s, 9H), 0.43 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  178.4, 144.5, 141.9, 137.7, 130.7, 129.1, 127.5, 67.3, 38.9, 27.4, 24.8, 3.3.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 2971 (w), 2904 (w), 1726 (m), 1698 (w), 1683 (w), 1558 (w), 1540 (w), 1507 (w), 1478 (w), 1456 (w), 1447 (w), 1417 (w), 1396 (w), 1363 (w), 1280 (w), 1251 (m), 1142 (s), 1057 (w), 1032 (w), 957 (w), 940 (w), 838 (m), 783 (m), 768 (m), 725 (w), 681 (w), 645 (w).

**HRMS:** Calcd. for  $\text{C}_{16}\text{H}_{26}\text{O}_2\text{SiNa}$ : 301.1594  $[\text{M}+\text{Na}]^+$ ; found ( $\text{ESI}^+$ ): 301.1586



### [3-Methyl-2-(trimethylsilyl)phenyl]methyl acetate (**155c**)

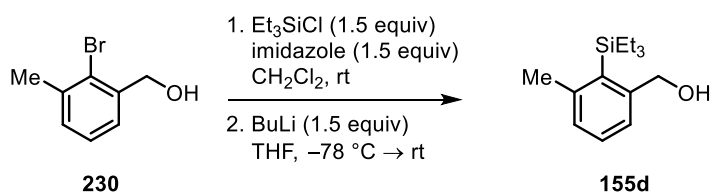
A 25 mL RBF fitted with magnetic stirrer bar and rubber septum was flame-dried and purged with N<sub>2</sub>. [3-Methyl-2-(trimethylsilyl)phenyl]methanol (180 mg, 0.9 mmol) was added followed by CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) and stirring commenced. Acetic anhydride (0.15 mL, 1.6 mmol) and triethylamine (0.23 mL, 1.6 mmol) were added *via* syringe, then 4-dimethylaminopyridine (DMAP, 12.2 mg, 10 mol%) added in one portion. After 14 hours, the reaction mixture was dry-loaded onto celite and purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (175 mg, 80%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.28 – 7.22 (m, 1H), 7.21 – 7.17 (m, 1H), 7.15 – 7.11 (m, 1H), 5.17 (s, 2H), 2.50 (s, 3H), 2.09 (s, 3H), 0.42 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 170.9, 144.8, 141.5, 138.1, 131.0, 129.1, 128.0, 67.7, 24.8, 21.3, 3.2.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2954 (w), 1736 (s), 1698 (w), 1472 (w), 1455 (w), 1447 (w), 1417 (w), 1376 (w), 1360 (w), 1230 (s), 1132 (w), 1023 (m), 966 (w), 836 (s), 785 (m), 765 (m), 724 (m), 681 (m), 657 (w), 633 (w), 606 (w).

**HRMS:** Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub>SiNa: 259.1125 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 259.1135



### [3-Methyl-2-(triethylsilyl)phenyl]methanol (**155d**)

(2-Bromo-3-methylphenyl)methanol (1.40 g, 7.0 mmol) was added to a flame-dried, N<sub>2</sub>-purged, round-bottomed flask containing a magnetic stirrer bar, and fitted with a rubber septum and inlet needle. CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added *via* syringe, followed by triethylsilyl

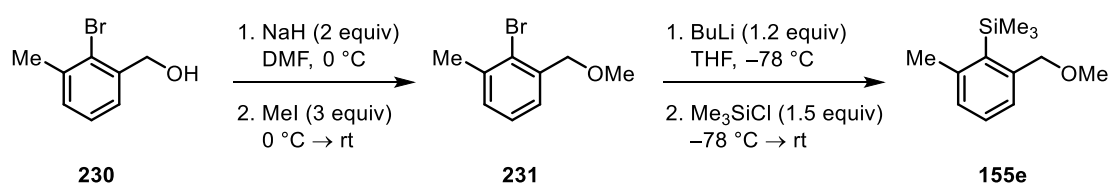
chloride (1.77 mL, 10.5 mmol) and imidazole (0.71 g, 10.5 mmol). The resulting solution was stirred for 15 hours at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (10 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, round-bottomed flask (again fitted with a septum and inlet needle). THF (20 mL) was added, and the solution cooled to −78 °C in an acetone-dry ice bath. *n*-Butyllithium (2.5 M in hexanes, 4.2 mL, 10.5 mmol) was added by syringe over approximately 15 minutes, and the solution allowed to return to room temperature overnight. After 14 hours, the mixture was quenched by the addition of H<sub>2</sub>O (20 mL) and extracted into Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the resulting crude oil purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (1.07 g, 65%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.30 – 7.22 (m, 2H), 7.12 – 7.06 (m, 1H), 4.72 (d, *J* = 5.6 Hz, 2H), 2.49 (s, 3H), 1.43 (br t, *J* = 5.7 Hz, 1H), 0.96 (app. s, 15H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 147.8, 145.2, 134.7, 130.3, 129.0, 126.3, 66.1, 24.6, 8.0, 6.2.

**ν<sub>max</sub>(neat)/cm<sup>−1</sup>:** 3307 (br w), 2952 (m), 2907 (w), 2873 (w), 1456 (w), 1445 (w), 1417 (w), 1396 (w), 1376 (w), 1237 (w), 1055 (w), 999 (m), 792 (w), 766 (w), 725 (m), 694 (m), 677 (m), 601 (w).

**HRMS:** Calcd. for C<sub>14</sub>H<sub>24</sub>OSiNa: 259.1489 [M+Na]<sup>+</sup>; found (ESI<sup>+</sup>): 259.1492



### 2-Bromo-1-(methoxymethyl)-3-methylbenzene (231)

A 150 mL RBF equipped with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> through an inlet needle. (2-Bromo-3-methylphenyl)methanol (2.01 g, 10.0 mmol) was added *via* syringe followed by anhydrous DMF (30 mL), and stirring commenced. The solution was cooled to 0 °C in an ice bath, then NaH (60% w/w dispersion in mineral oil, 0.80 g, 20.0 mmol) was added portion-wise. Following addition, the reaction mixture was stirred for 45 minutes at 0 °C, then methyl iodide (1.87 mL, 30.0 mmol) added *via* syringe in one

portion. The mixture was allowed to return to room temperature and stirred for a further 3 hours. The reaction was quenched by addition of H<sub>2</sub>O (10 mL), then extracted into Et<sub>2</sub>O (3 × 50 mL). The combined organic extracts were washed with NaOH (3.0 M, 30 mL) then brine (30 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford the title compound as a clear, colourless oil without the need for additional purification (1.81 g, 84%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.32 – 7.27 (m, 1H), 7.25 – 7.15 (m, 2H), 4.54 (s, 2H), 3.48 (s, 3H), 2.42 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 138.5, 138.1, 129.9, 127.1, 126.4, 125.3, 74.7, 58.8, 23.6.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2922 (w), 2853 (w), 2818 (w), 1683 (w), 1557 (w), 1540 (w), 1507 (w), 1455 (w), 1417 (w), 1379 (w), 1365 (w), 1195 (w), 1114 (m), 1098 (m), 1026 (m), 979 (w), 955 (w), 936 (w), 906 (w), 891 (w), 771 (m), 720 (w), 702 (w), 656 (w).

**HRMS:** Calcd. for C<sub>9</sub>H<sub>11</sub>O<sup>79</sup>Br: 213.9988 [M]<sup>+</sup>; found (EI<sup>+</sup>): 213.9978

#### **[2-(Methoxymethyl)-6-methylphenyl]trimethylsilane (155e)**

A 150 mL RBF fitted with stirrer bar and rubber septum was flame-dried, then purged with N<sub>2</sub> *via* an inlet needle. 2-Bromo-1-(methoxymethyl)-3-methylbenzene (1.81 g, 8.4 mmol) and THF (20 mL) were added *via* syringe, stirring commenced, and the temperature adjusted to –78 °C with an external acetone-dry ice bath. *n*-Butyllithium (2.3 M in hexanes, 4.35 mL, 10.0 mmol) was added dropwise over 20 minutes. The solution was stirred for a further 45 minutes at –78 °C, then trimethylsilyl chloride (1.52 mL, 12.0 mmol) added *via* syringe in one portion. The reaction mixture was allowed to return to room temperature overnight. The reaction was quenched by addition of H<sub>2</sub>O (10 mL) and extracted into Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated in vacuo, and the residue purified by column chromatography (eluent: 100:0 → 90:10 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (1.70 g, 97%).

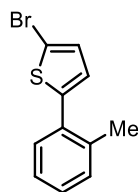
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.25 – 7.16 (m, 2H), 7.11 – 7.06 (m, 1H), 4.49 (s, 2H), 3.34 (s, 3H), 2.49 (s, 3H), 0.41 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 144.5, 144.1, 137.3, 130.2, 128.7, 127.1, 75.6, 57.7, 24.7, 3.0.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 2977 (w), 2950 (w), 2926 (w), 2894 (w), 1456 (w), 1446 (w), 1417 (w), 1380 (w), 1248 (m), 1190 (w), 1130 (w), 1091 (m), 1056 (w), 926 (w), 837 (m), 790 (m), 761 (m), 724 (m), 680 (w), 643 (w), 622 (w).

**HRMS:** Calcd. for  $\text{C}_{12}\text{H}_{20}\text{OSi}$ : 208.1278  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 208.1262

### 5.4.3 Arylation Products



#### 2-Bromo-5-(2-methylphenyl)thiophene (232)

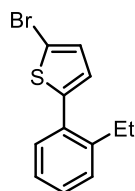
Analytical sample prepared according to General Procedure C (PTLC eluent: hexanes).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.38 – 7.31 (m, 1H), 7.29 – 7.18 (m, 3H), 7.04 (d,  $J = 3.8$  Hz, 1H), 6.81 (d,  $J = 3.8$  Hz, 1H), 2.42 (s, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  144.9, 136.3, 133.5, 131.0, 130.4, 130.1, 128.4, 126.8, 126.2, 111.7, 21.1.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 1507 (m), 1486 (m), 1455 (w), 1429 (w), 1378 (w), 1204 (w), 976 (m), 936 (w), 798 (m), 754 (s), 733 (w), 720 (m), 679 (w), 450 (w), 422 (w).

$^1\text{H}$  and  $^{13}\text{C}$  NMR data are consistent with those reported in the literature.<sup>5</sup>



#### 2-Bromo-5-(2-ethylphenyl)thiophene (233)

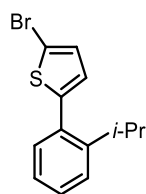
Analytical sample prepared according to General Procedure C (PTLC eluent: hexanes).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.35 – 7.28 (m, 3H), 7.24 – 7.18 (m, 1H), 7.03 (d, *J* = 3.7 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 1H), 2.74 (q, *J* = 7.5 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 144.7, 142.8, 133.0, 131.0, 130.0, 129.2, 128.8, 126.8, 125.9, 111.6, 26.6, 15.9.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2964 (w), 2928 (w), 2870 (w), 1558 (w), 1541 (w), 1507 (w), 1484 (w), 1447 (w), 1430 (w), 1373 (w), 1202 (w), 1054 (w), 978 (m), 937 (w), 796 (m), 755 (m), 733 (w), 675 (w).

**HRMS:** Calcd. for C<sub>12</sub>H<sub>11</sub><sup>79</sup>BrS: 265.9759 [M]<sup>+</sup>; found (EI<sup>+</sup>): 265.9748



## 2-Bromo-5-[2-(propan-2-yl)phenyl]thiophene (234)

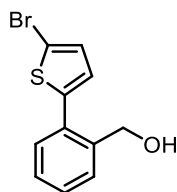
Analytical sample prepared according to General Procedure C (PTLC eluent: hexanes).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.41 – 7.33 (m, 2H), 7.30 – 7.27 (m, 1H), 7.22 – 7.16 (m, 1H), 7.03 (d, *J* = 3.7 Hz, 1H), 6.73 (d, *J* = 3.7 Hz, 1H), 3.27 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 147.9, 144.7, 132.3, 131.2, 129.9, 129.1, 127.0, 126.0, 125.6, 111.6, 29.7, 24.5.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2960 (w), 2924 (w), 1557 (w), 1540 (w), 1507 (w), 1483 (w), 1456 (w), 1446 (w), 1431 (w), 1362 (w), 1205 (w), 1088 (w), 1054 (w), 1032 (w), 977 (m), 938 (w), 796 (m), 757 (m), 731 (w), 676 (w), 503 (w), 464 (w).

**HRMS:** Calcd. for C<sub>13</sub>H<sub>13</sub><sup>79</sup>BrS: 279.9916 [M]<sup>+</sup>; found (EI<sup>+</sup>): 279.9905



**[2-(5-Bromothiophen-2-yl)phenyl]methanol (154a)**

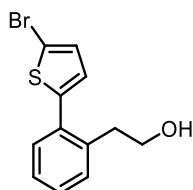
Prepared according to General Procedure A (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 3:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (161 mg, 60%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 – 7.51 (m, 1H), 7.43 – 7.31 (m, 3H), 7.06 (d, *J* = 3.8 Hz, 1H), 6.95 (d, *J* = 3.8 Hz, 1H), 4.73 (s, 2H), 1.70 (br s, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.3, 138.6, 133.1, 130.8, 130.4, 129.2, 128.8, 128.2, 127.5, 112.4, 63.5.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3294 (br w), 3060 (w), 2921 (w), 2883 (w), 1480 (w), 1449 (w), 1431 (m), 1310 (w), 1193 (w), 1161 (w), 1096 (w), 1028 (w), 999 (m), 977 (m), 938 (w), 798 (w), 755 (s), 688 (m), 633 (w), 590 (w), 575 (w), 530 (w), 516 (m), 504 (m), 441 (w), 420 (w).

**HRMS:** Calcd. for C<sub>11</sub>H<sub>9</sub>O<sup>79</sup>BrS: 267.9552 [M]<sup>+</sup>; found (EI<sup>+</sup>): 267.9567



**2-[2-(5-Bromothiophen-2-yl)phenyl]ethan-1-ol (154b)**

Prepared according to General Procedure A (reaction time: 12 hours). The residue was purified by column chromatography (eluent: 80:20 hexanes/EtOAc) to afford the title compound as a yellow oil (152 mg, 54%).

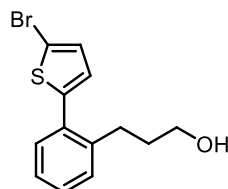
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.36 – 7.32 (m, 3H), 7.29 – 7.23 (m, 1H), 7.03 (d, *J* = 3.8 Hz, 1H), 6.80 (d, *J* = 3.8 Hz, 1H), 3.79 (t, *J* = 6.9 Hz, 2H), 3.00 (t, *J* = 6.9 Hz, 2H), 1.40 (br s, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 144.2, 137.1, 133.9, 131.5, 130.4, 130.1, 128.8, 127.2, 126.7, 112.0, 63.5, 36.6.



$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3306 (br w), 2931 (w), 2873 (w), 1483 (w), 1447 (w), 1431 (m), 1198 (w), 1040 (m), 977 (m), 938 (w), 797 (m), 755 (s), 683 (w), 587 (w), 575 (w), 516 (w), 489 (w).

**HRMS:** Calcd. for  $\text{C}_{12}\text{H}_{11}\text{O}^{79}\text{BrS}$ : 281.9709  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 281.9716



### 3-[2-(5-Bromothiophen-2-yl)phenyl]propan-1-ol (154c)

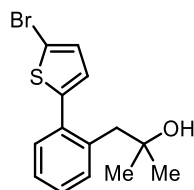
Prepared according to General Procedure A (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 3:1 hexanes/EtOAc) to afford the title compound as a viscous, pale yellow oil (237 mg, 80%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.34 – 7.28 (m, 3H), 7.25 – 7.20 (m, 1H), 7.03 (d,  $J = 3.7$  Hz, 1H), 6.78 (d,  $J = 3.7$  Hz, 1H), 3.62 (t,  $J = 6.8$  Hz, 2H), 2.86 – 2.77 (m, 2H), 1.85 – 1.76 (m, 2H), 1.31 (br s, 1H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  144.5, 140.5, 133.2, 131.3, 130.1, 129.9, 128.8, 126.9, 126.2, 111.8, 62.5, 34.4, 29.8.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3308 (br w), 2932 (w), 2866 (w), 1483 (w), 1447 (w), 1431 (w), 1200 (w), 1161 (w), 1054 (m), 977 (m), 940 (w), 796 (m), 755 (m), 681 (w), 575 (w), 516 (w), 420 (w).

**HRMS:** Calcd. for  $\text{C}_{13}\text{H}_{13}\text{O}^{79}\text{BrS}$ : 295.9865  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 295.9867



### 1-[2-(5-Bromothiophen-2-yl)phenyl]-2-methylpropan-2-ol (154p)

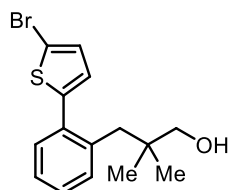
Analytical sample prepared according to General Procedure C (PTLC eluent: 3:1 hexanes/EtOAc).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.47 – 7.41 (m, 1H), 7.39 – 7.32 (m, 2H), 7.32 – 7.26 (m, 1H), 7.04 (d,  $J = 3.7$  Hz, 1H), 6.84 (d,  $J = 3.7$  Hz, 1H), 3.04 (s, 2H), 1.15 (s, 6H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  145.3, 136.7, 134.7, 131.9, 131.7, 130.1, 128.3, 127.5, 126.8, 112.0, 71.7, 45.4, 29.7.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 3339 (w, br), 2977 (w), 2964 (w), 2919 (w), 2849 (w), 1487 (w), 1472 (w), 1457 (w), 1446 (m), 1420 (w), 1377 (w), 1362 (m), 1316 (w), 1229 (w), 1197 (w), 1155 (m), 1142 (m), 1131 (m), 974 (m), 894 (m), 831 (w), 806 (m), 773 (w), 759 (s), 722 (w), 682 (m), 618 (w), 591 (w), 521 (w), 493 (w).

**HRMS:** Calcd. for  $\text{C}_{14}\text{H}_{15}\text{O}^{79}\text{BrS}$ : 300.0022  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 300.0032



**3-[2-(5-Bromothiophen-2-yl)phenyl]-2,2-dimethylpropan-1-ol (154q)**

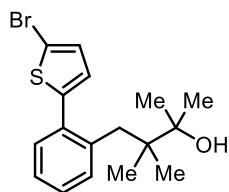
Analytical sample prepared according to General Procedure C (PTLC eluent: 4:1 hexanes/EtOAc).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.37 – 7.17 (m, 4H), 7.05 (d,  $J$  = 3.8 Hz, 1H), 6.80 (d,  $J$  = 3.7 Hz, 1H), 3.21 (s, 2H), 2.90 (s, 2H), 0.77 (s, 6H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  145.6, 137.5, 134.3, 132.3, 131.5, 129.9, 127.8, 127.2, 126.3, 111.7, 71.1, 40.0, 37.6, 24.2.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 3335 (w, br), 2955 (w), 2922 (w), 2867 (w), 1472 (w), 1457 (w), 1446 (w), 1430 (w), 1387 (w), 1363 (w), 1201 (w), 1037 (m), 977 (m), 940 (w), 797 (w), 759 (m), 723 (w), 684 (w), 670 (w), 594 (w).

**HRMS:** Calcd. for  $\text{C}_{15}\text{H}_{17}\text{O}^{79}\text{BrS}$ : 324.0178  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 324.0174



#### 4-[2-(5-Bromothiophen-2-yl)phenyl]-2,3,3-trimethylbutan-2-ol (154r)

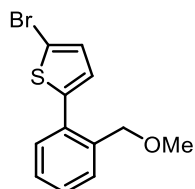
Analytical sample prepared according to General Procedure C (PTLC eluent: 4:1 hexanes/EtOAc).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.35 – 7.23 (m, 4H), 7.03 (d, *J* = 3.7 Hz, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 3.03 (s, 2H), 1.19 (s, 6H), 0.70 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 146.0, 138.6, 135.0, 132.8, 131.6, 129.9, 127.7, 127.3, 126.3, 111.6, 75.7, 42.6, 37.7, 25.5, 21.6.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2971 (w), 1472 (w), 1456 (w), 1447 (w), 1431 (w), 1374 (w), 1264 (w), 1200 (w), 1163 (w), 1129 (w), 1109 (w), 1079 (w), 978 (m), 940 (w), 872 (w), 799 (w), 759 (m), 737 (m), 704 (w), 687 (w), 504 (w).

**HRMS:** Calcd. for C<sub>17</sub>H<sub>21</sub>O<sup>79</sup>BrS: 352.0491 [M]<sup>+</sup>; found (EI<sup>+</sup>): 352.0497



#### 2-Bromo-5-[2-(methoxymethyl)phenyl]thiophene (154e)

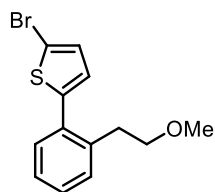
Prepared according to General Procedure B (reaction time: 1 hour). The residue was purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (127 mg, 90%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.55 – 7.51 (m, 1H), 7.45 – 7.34 (m, 3H), 7.08 (d, *J* = 3.8 Hz, 1H), 6.95 (d, *J* = 3.8 Hz, 1H), 4.46 (s, 2H), 3.43 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.5, 135.8, 133.7, 130.7, 130.3, 130.2, 128.5, 128.3, 127.5, 112.4, 72.9, 58.2.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 2921 (w), 2869 (w), 2819 (w), 1484 (w), 1448 (w), 1430 (w), 1380 (w), 1191 (w), 1117 (w), 1090 (m), 978 (m), 960 (w), 938 (w), 907 (w), 840 (w), 798 (m), 757 (m), 684 (w), 616 (w), 590 (w), 516 (w), 487 (w), 443 (w), 418 (w).

**HRMS:** Calcd. for  $\text{C}_{12}\text{H}_{11}\text{O}^{79}\text{BrS}$ : 281.9709  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 281.9713



**2-Bromo-5-[2-(2-methoxyethyl)phenyl]thiophene (154f)**

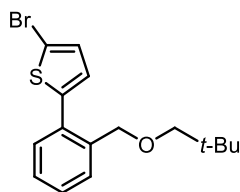
Prepared according to General Procedure A (reaction time: 10 hours). The residue was purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (282 mg, 95%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.36 – 7.29 (m, 3H), 7.27 – 7.21 (m, 1H), 7.03 (d,  $J = 3.7$  Hz, 1H), 6.80 (d,  $J = 3.7$  Hz, 1H), 3.54 (t,  $J = 7.2$  Hz, 2H), 3.31 (s, 3H), 3.00 (t,  $J = 7.2$  Hz, 2H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  144.3, 137.5, 133.7, 131.2, 130.3, 130.1, 128.7, 127.1, 126.5, 111.8, 73.3, 58.8, 33.6.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 2922 (w), 2869 (w), 2823 (w), 2805 (w), 1485 (w), 1448 (w), 1431 (w), 1381 (w), 1197 (w), 1110 (m), 1054 (w), 997 (w), 977 (m), 938 (w), 797 (m), 757 (m), 679 (w), 586 (w), 517 (w), 495 (w).

**HRMS:** Calcd. for  $\text{C}_{13}\text{H}_{13}\text{O}^{79}\text{BrS}$ : 295.9865  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 295.9875



### 2-Bromo-5-{2-[(2,2-dimethylpropoxy)methyl]phenyl}thiophene (154g)

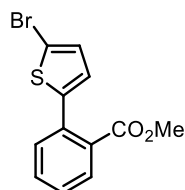
Prepared according to General Procedure B (reaction time: 12 hours). The residue was purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (154 mg, 91%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.58 – 7.51 (m, 1H), 7.41 – 7.29 (m, 3H), 7.04 (d, *J* = 3.8 Hz, 1H), 6.92 (d, *J* = 3.8 Hz, 1H), 4.50 (s, 2H), 3.13 (s, 2H), 0.94 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.7, 136.7, 133.3, 130.5, 130.3, 129.8, 128.4, 127.9, 127.5, 112.2, 81.2, 71.5, 32.3, 27.0.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2952 (w), 2899 (w), 2864 (w), 1476 (w), 1450 (w), 1431 (w), 1384 (w), 1361 (w), 1200 (w), 1122 (w), 1086 (m), 1046 (w), 978 (m), 940 (w), 797 (m), 757 (m), 734 (w), 682 (w).

**HRMS:** Calcd. for C<sub>16</sub>H<sub>19</sub>O<sup>79</sup>BrS: 338.0335 [M]<sup>+</sup>; found (EI<sup>+</sup>): 338.0320



### Methyl 2-(5-bromothiophen-2-yl)benzoate (154h)

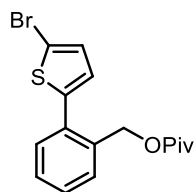
Prepared according to General Procedure B (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (76 mg, 51%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.77 – 7.72 (m, 1H), 7.53 – 7.47 (m, 1H), 7.45 – 7.38 (m, 2H), 7.01 (d, *J* = 3.8 Hz, 1H), 6.78 (d, *J* = 3.8 Hz, 1H), 3.77 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 168.7, 143.7, 133.5, 131.6, 131.4, 131.3, 130.2, 129.9, 128.3, 126.8, 112.5, 52.5.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 1718 (s), 1683 (w), 1595 (w), 1484 (w), 1447 (w), 1429 (m), 1289 (m), 1252 (m), 1189 (w), 1124 (m), 1086 (m), 1058 (w), 1044 (w), 978 (m), 963 (w), 942 (w), 824 (w), 796 (m), 757 (m), 713 (w), 704 (w), 658 (w).

**HRMS:** Calcd. for  $\text{C}_{12}\text{H}_9\text{O}_2^{79}\text{BrS}$ : 295.9501  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 295.9503



**[2-(5-Bromothiophen-2-yl)phenyl]methyl 2,2-dimethylpropanoate (154i)**

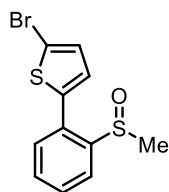
Prepared according to General Procedure B (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (146 mg, 83%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.53 – 7.48 (m, 1H), 7.45 – 7.36 (m, 3H), 7.06 (d,  $J = 3.8$  Hz, 1H), 6.87 (d,  $J = 3.8$  Hz, 1H), 5.17 (d,  $J = 0.5$  Hz, 2H), 1.23 (s, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  178.3, 143.1, 134.3, 133.8, 130.9, 130.3, 130.1, 128.7, 128.6, 127.4, 112.6, 64.5, 39.0, 27.3.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 2969 (w), 1725 (m), 1698 (w), 1683 (w), 1540 (w), 1478 (w), 1455 (w), 1431 (w), 1396 (w), 1363 (w), 1277 (m), 1203 (w), 1139 (s), 1032 (w), 978 (m), 939 (w), 798 (w), 758 (m), 682 (w).

**HRMS:** Calcd. for  $\text{C}_{16}\text{H}_{17}\text{O}_2^{79}\text{BrS}$ : 352.0127  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 352.0136



### 2-Bromo-5-(2-methanesulfinylphenyl)thiophene (154j)

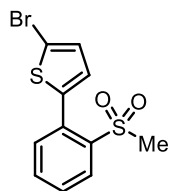
Prepared according to General Procedure A (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 1:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (226 mg, 75%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  8.12 (ddd,  $J$  = 7.9, 1.4, 0.4 Hz, 1H), 7.62 (ddd,  $J$  = 7.9, 7.4, 1.3 Hz, 1H), 7.51 (app. td,  $J$  = 7.5, 1.4 Hz, 1H), 7.40 (ddd,  $J$  = 7.6, 1.3, 0.4 Hz, 1H), 7.07 (d,  $J$  = 3.8 Hz, 1H), 6.93 (d,  $J$  = 3.8 Hz, 1H), 2.54 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  144.7, 140.3, 131.0, 130.9, 130.9, 130.8, 129.9, 128.2, 124.1, 114.1, 42.3.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 1468 (m), 1436 (w), 1425 (w), 1250 (w), 1200 (w), 1070 (m), 1038 (m), 977 (m), 951 (w), 939 (m), 841 (w), 800 (w), 761 (m), 734 (w), 711 (w), 673 (w), 660 (w), 514 (w), 489 (w), 472 (w), 419 (w).

**HRMS:** Calcd. for C<sub>11</sub>H<sub>9</sub>O<sup>79</sup>BrS<sub>2</sub>: 299.9273 [M]<sup>+</sup>; found (EI<sup>+</sup>): 299.9291



### 2-Bromo-5-(2-methanesulfonylphenyl)thiophene (154k)

Prepared according to General Procedure A (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 3:1 hexanes/EtOAc) to afford the title compound as a white solid (272 mg, 86%).

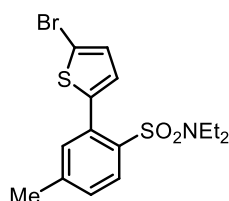
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  8.25 (dd,  $J$  = 8.0, 1.5 Hz, 1H), 7.64 (app. td,  $J$  = 7.5, 1.6 Hz, 1H), 7.58 (app. td,  $J$  = 7.7, 1.5 Hz, 1H), 7.50 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.23 (d,  $J$  = 3.8 Hz, 1H), 7.09 (d,  $J$  = 3.9 Hz, 1H), 2.81 (s, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  140.0, 139.5, 133.8, 133.3, 132.8, 131.3, 130.6, 129.2, 129.1, 114.4, 42.7.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2922 (w), 1466 (w), 1439 (w), 1426 (w), 1297 (s), 1248 (m), 1199 (w), 1169 (w), 1144 (s), 1125 (m), 1068 (m), 1058 (m), 1040 (w), 970 (m), 953 (m), 938 (m), 885 (w), 811 (m), 778 (m), 761 (s), 732 (m), 663 (m), 591 (w), 537 (s), 510 (s), 465 (m), 421 (m).

**HRMS:** Calcd. for  $\text{C}_{11}\text{H}_9\text{O}_2^{79}\text{BrS}_2$ : 315.9222  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 315.9237

**mp:** 126 – 128 °C (hexanes/EtOAc)



**2-(5-Bromothiophen-2-yl)-N,N-diethyl-4-methylbenzene-1-sulfonamide (154l)**

Prepared according to General Procedure A (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 4:1 hexanes/EtOAc) to afford the title compound as an orange oil that crystallised on standing overnight (307 mg, 79%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.98 (d,  $J$  = 8.1 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.08 (d,  $J$  = 3.8 Hz, 1H), 7.02 (d,  $J$  = 3.8 Hz, 1H), 2.98 (q,  $J$  = 7.1 Hz, 4H), 2.41 (s, 3H), 1.00 (t,  $J$  = 7.1 Hz, 6H).

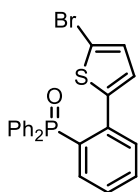
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  142.9, 141.0, 137.1, 134.8, 132.6, 130.7, 130.0, 129.9, 129.2, 112.8, 41.0, 21.3, 14.0.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2972 (w), 2932 (w), 2869 (w), 1601 (w), 1569 (w), 1458 (w), 1437 (w), 1386 (w), 1360 (w), 1320 (m), 1266 (w), 1203 (m), 1180 (w), 1163 (m), 1135 (m), 1099 (w), 1075 (m), 1058 (w), 1017 (m), 986 (w), 958 (w), 944 (m), 889 (w), 837 (m), 807 (m), 789 (m), 778 (m), 740 (w), 709 (m), 678 (m), 646 (m), 632 (w), 599 (m), 568 (w), 546 (m), 503 (m), 465 (w), 437 (w), 420 (w).

**HRMS:** Calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}_2\text{N}^{79}\text{BrS}_2$ : 386.9957  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 386.9951

**mp:** 74 – 77 °C (hexanes/EtOAc)





### 2-Bromo-5-[2-(diphenylphosphoroso)phenyl]thiophene (154m)

Prepared according to General Procedure B (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 1:1 hexanes/EtOAc) to afford the title compound as a white solid (175 mg, 80%).

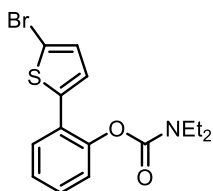
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.67 – 7.29 (m, 14H), 7.19 (d,  $J$  = 3.8 Hz, 1H), 6.69 (d,  $J$  = 3.9 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  142.5 (d,  $J$  = 4.9 Hz), 138.6 (d,  $J$  = 7.7 Hz), 134.6 (d,  $J$  = 11.9 Hz), 132.8 (d,  $J$  = 101.7 Hz), 132.6 (d,  $J$  = 9.2 Hz), 132.4 (d,  $J$  = 101.3 Hz), 131.9 (d,  $J$  = 1.2 Hz), 131.6 (d,  $J$  = 9.4 Hz), 131.4 (d,  $J$  = 2.7 Hz), 131.0 (s), 129.7 (s), 128.3 (d,  $J$  = 12.2 Hz), 127.6 (d,  $J$  = 12.3 Hz), 113.4 (s).

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 3076 (w), 3055 (w), 2923 (w), 1586 (w), 1562 (w), 1467 (w), 1436 (m), 1320 (w), 1303 (w), 1261 (w), 1188 (m), 1135 (w), 1103 (m), 1068 (w), 1027 (w), 999 (w), 977 (m), 938 (m), 885 (w), 822 (m), 774 (m), 753 (w), 717 (s), 693 (s), 665 (m), 632 (w), 534 (s), 507 (m), 490 (m), 456 (m).

**HRMS:** Calcd. for C<sub>22</sub>H<sub>16</sub>O<sup>79</sup>BrPS: 437.9837 [M]<sup>+</sup>; found (EI<sup>+</sup>): 437.9838

**mp:** 150 – 153 °C (hexanes/EtOAc)



### 2-(5-Bromothiophen-2-yl)phenyl N,N-diethylcarbamate (154n)

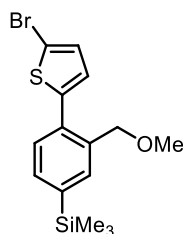
Prepared according to General Procedure A (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 17:1 hexanes/EtOAc) to afford the title compound as a pale yellow oil (255 mg, 72%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.54 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.32 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 7.23 (app. td, *J* = 7.6, 1.4 Hz, 1H), 7.15 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.04 – 7.01 (m, 2H), 3.50 (q, *J* = 7.1 Hz, 2H), 3.38 (q, *J* = 7.1 Hz, 2H) 1.29 – 1.13 (m, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 153.8, 148.0, 140.3, 129.9, 129.2, 129.0, 127.1, 126.1, 125.9, 123.8, 112.7, 42.3, 41.9, 14.3, 13.4.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2972 (w), 2932 (w), 1714 (s), 1562 (w), 1506 (w), 1487 (w), 1472 (w), 1456 (w), 1416 (m), 1379 (w), 1365 (w), 1349 (w), 1315 (w), 1266 (m), 1236 (w), 1194 (m), 1147 (m), 1101 (m), 1075 (w), 1036 (w), 980 (m), 958 (m), 933 (m), 821 (w), 787 (m), 749 (m), 679 (w), 447 (w).

**HRMS:** Calcd. for C<sub>15</sub>H<sub>16</sub>O<sub>2</sub>N<sup>79</sup>BrS: 353.0080 [M]<sup>+</sup>; found (EI<sup>+</sup>): 353.0089



**[4-(5-Bromothiophen-2-yl)-3-(methoxymethyl)phenyl]trimethylsilane (154o)**

Prepared according to General Procedure A (reaction time: 10 hours). The residue was purified by column chromatography (eluent: 95:5 → 90:10 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (259 mg, 73%).

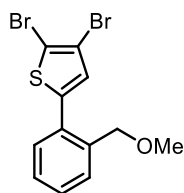
*Regioselectivity was confirmed by additional 2D NMR experiments.*

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.63 (dd, *J* = 1.3, 0.5 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.39 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.05 (d, *J* = 3.8 Hz, 1H), 6.95 (d, *J* = 3.8 Hz, 1H), 4.43 (s, 2H), 3.42 (s, 3H), 0.30 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.7, 141.1, 135.4, 134.6, 134.3, 133.4, 130.4, 129.9, 127.6, 112.5, 73.2, 58.2, -1.0.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2953 (w), 2921 (w), 2890 (w), 1557 (w), 1540 (w), 1506 (w), 1487 (w), 1472 (w), 1456 (w), 1434 (w), 1418 (w), 1386 (w), 1371 (w), 1247 (m), 1191 (w), 1112 (w), 1089 (m), 978 (m), 947 (w), 881 (m), 826 (s), 797 (m), 753 (m), 694 (w), 654 (w), 623 (w), 596 (w), 553 (w), 508 (w), 472 (w).

**HRMS:** Calcd. for  $C_{15}H_{19}O^{79}BrSSi$ : 354.0104  $[M]^+$ ; found (EI<sup>+</sup>): 354.0101



**2,3-Dibromo-5-[2-(methoxymethyl)phenyl]thiophene (157b)**

Prepared according to General Procedure B (reaction time: 6 hours). The residue was purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a pale yellow solid (138 mg, 76%).

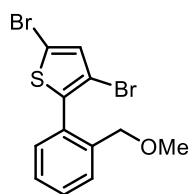
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.53 – 7.48 (m, 1H), 7.42 – 7.33 (m, 3H), 7.01 (s, 1H), 4.42 (s, 2H), 3.42 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  143.3, 135.9, 133.0, 130.4, 129.7, 129.0, 128.5, 114.0, 111.4, 72.8, 58.1.

**$\nu_{\text{max}}$ (neat)/cm<sup>-1</sup>:** 2975 (w), 2917 (w), 2889 (w), 2823 (w), 2805 (w), 1525 (w), 1474 (m), 1459 (w), 1447 (m), 1380 (m), 1315 (m), 1203 (w), 1186 (m), 1142 (w), 1084 (s), 1045 (m), 997 (m), 953 (m), 936 (m), 835 (m), 815 (m), 754 (s), 744 (s), 692 (m), 619 (w), 590 (m), 510 (w), 499 (w), 451 (w), 418 (w).

**HRMS:** Calcd. for  $C_{12}H_{10}O^{79}Br_2S$ : 359.8814  $[M]^+$ ; found (EI<sup>+</sup>): 359.8813

**mp:** 51 – 53 °C (hexanes/EtOAc)



### 3,5-Dibromo-2-[2-(methoxymethyl)phenyl]thiophene (157c)

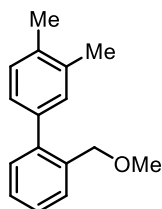
Prepared according to General Procedure B (reaction time: 12 hours). The residue was purified by column chromatography (eluent: 100:0 → 95:5 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (150 mg, 83%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.56 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.46 (app. td, *J* = 7.5, 1.5 Hz, 1H), 7.35 (app. td, *J* = 7.5, 1.5 Hz, 1H), 7.29 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.03 (s, 1H), 4.38 (s, 2H), 3.34 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 138.5, 138.3, 132.4, 131.6, 130.6, 129.8, 128.5, 127.6, 112.6, 109.7, 72.1, 58.5.

**ν<sub>max</sub>(neat)/cm<sup>-1</sup>:** 2921 (w), 2885 (w), 2819 (w), 1480 (w), 1450 (m), 1434 (w), 1378 (w), 1363 (w), 1301 (w), 1194 (w), 1116 (m), 1092 (m), 1044 (w), 981 (m), 943 (w), 921 (w), 874 (w), 816 (m), 756 (m), 725 (w), 693 (w), 654 (w), 629 (w), 607 (w), 523 (w), 444 (w).

**HRMS:** Calcd. for C<sub>12</sub>H<sub>10</sub>O<sup>79</sup>Br<sub>2</sub>S: 359.8814 [M]<sup>+</sup>; found (EI<sup>+</sup>): 359.8809



### 2-(Methoxymethyl)-3',4'-dimethyl-1,1'-biphenyl (157d)

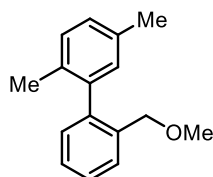
Prepared according to General Procedure B (reaction time: 24 hours). The residue was purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (87 mg, 77%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.56 – 7.50 (m, 1H), 7.39 – 7.27 (m, 3H), 7.21 – 7.09 (m, 3H), 4.36 (s, 2H), 3.35 (s, 3H), 2.35 – 2.29 (m, 6H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  142.0, 138.5, 136.4, 135.6, 130.7, 130.1, 129.5, 129.1, 127.7, 127.3, 126.8, 72.7, 58.2, 20.0, 19.6.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2920 (w), 1558 (w), 1541 (w), 1507 (w), 1480 (w), 1447 (w), 1419 (w), 1395 (w), 1380 (w), 1338 (w), 1321 (w), 1195 (w), 1114 (w), 1085 (m), 1021 (w), 987 (w), 946 (w), 889 (w), 827 (w), 763 (m), 720 (w), 638 (w), 601 (w), 554 (w).

**HRMS:** Calcd. for  $\text{C}_{16}\text{H}_{18}\text{O}$ : 226.1352  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 226.1362



**2'-(Methoxymethyl)-2,5-dimethyl-1,1'-biphenyl (157e)**

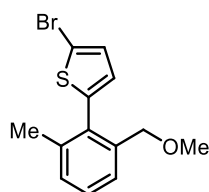
Prepared according to General Procedure B (reaction time: 36 hours). The residue was purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (35 mg, 31%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.57 – 7.51 (m, 1H), 7.37 (app. td,  $J$  = 7.5, 1.5 Hz, 1H), 7.31 (app. td,  $J$  = 7.4, 1.6 Hz, 1H), 7.19 – 7.05 (m, 3H), 6.97 – 6.92 (m, 1H), 4.17 (s, 2H), 3.26 (s, 3H), 2.34 (s, 3H), 2.01 (s, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  141.0, 140.2, 136.2, 134.9, 132.9, 130.3, 129.8, 129.6, 128.2, 127.9, 127.4, 127.3, 72.3, 58.4, 21.1, 19.6.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2919 (w), 2863 (w), 2819 (w), 1480 (w), 1447 (w), 1378 (w), 1192 (w), 1114 (w), 1093 (m), 1046 (w), 971 (w), 944 (w), 923 (w), 887 (w), 810 (m), 772 (m), 744 (m), 634 (w), 611 (w), 468 (w).

**HRMS:** Calcd. for  $\text{C}_{16}\text{H}_{18}\text{O}$ : 226.1352  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 226.1354



### 2-Bromo-5-[2-(methoxymethyl)-6-methylphenyl]thiophene (158e)

Prepared according to General Procedure B (reaction time: 16 hours). The residue was purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a clear, colourless oil (208 mg, 69%).

*Note: Purity estimated to be approximately 90% by  $^1\text{H}$  NMR, containing impurities arising from protodesilylation and bromodesilylation of the arylsilane.*

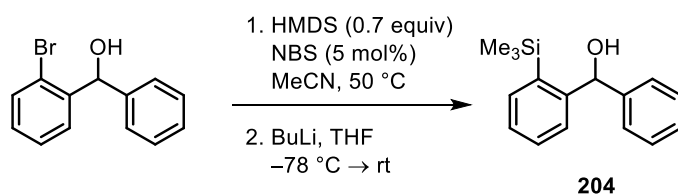
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.40 – 7.27 (m, 2H), 7.23 – 7.18 (m, 1H), 7.06 (d,  $J$  = 3.6 Hz, 1H), 6.63 (d,  $J$  = 3.6 Hz, 1H), 4.25 (s, 2H), 3.31 (s, 3H), 2.19 (s, 2H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  141.5, 138.6, 138.6, 132.3, 130.0, 129.4, 129.0, 127.7, 125.8, 112.0, 72.6, 58.4, 20.7.

**$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$ :** 2920 (w), 2887 (w), 2817 (w), 1463 (m), 1446 (m), 1420 (w), 1378 (w), 1222 (w), 1190 (m), 1166 (w), 1091 (m), 1052 (w), 1019 (w), 975 (m), 955 (w), 936 (w), 912 (w), 896 (w), 794 (m), 777 (m), 728 (w), 673 (w), 635 (w), 606 (w), 517 (w).

**HRMS:** Calcd. for  $\text{C}_{13}\text{H}_{13}\text{O}^{79}\text{BrS}$ : 295.9865  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 295.9853

### 5.4.4 Synthesis of Restricted Rotation Arylsilane Traps



### Phenyl[2-(trimethylsilyl)phenyl]methanol (204)

(2-Bromophenyl)(phenyl)methanol (1.32 g, 5.0 mmol) was added to a flame-dried,  $\text{N}_2$ -purged, 100 mL RBF containing a magnetic stirrer bar, and fitted with a rubber septum and inlet

needle. MeCN (12.5 mL) was added *via* syringe, followed by hexamethyldisilazane (HMDS, 0.73 mL, 3.5 mmol). The resulting solution was stirred for 15 mins at room temperature, then *N*-bromosuccinimide (NBS, 45 mg, 0.25 mmol) added in one portion. The temperature was adjusted to 50 °C and stirring maintained for a further 2 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (5 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a second flame-dried, N<sub>2</sub>-purged, 100 mL RBF (again fitted with a septum and inlet needle). THF (6 mL) was added, and the solution cooled to −78 °C in an acetone-dry ice bath. *n*-Butyllithium (2.15 M in hexanes, 1.4 mL, 3.0 mmol) was added by syringe over approximately 10 minutes, and the solution allowed to return to room temperature overnight. The mixture was quenched by the addition of H<sub>2</sub>O (10 mL) and extracted into Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated *in vacuo*, and the resulting solid purified by column chromatography (eluent: 9:1 hexane/EtOAc) to afford the title compound as a pale yellow solid (0.51 g, 40%).

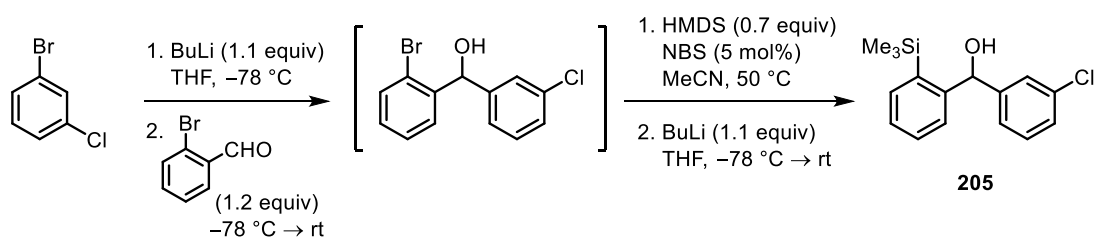
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.57 (ddd, *J* = 7.3, 1.7, 0.6 Hz, 1H), 7.37 – 7.21 (m, 8H), 6.15 (d, *J* = 4.0 Hz, 1H), 2.06 (d, *J* = 4.1 Hz, 1H), 0.39 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 149.5, 143.8, 139.0, 134.6, 130.0, 128.3, 128.2, 127.4, 127.3, 126.7, 74.8, 0.9.

***v*<sub>max</sub>(neat)/cm<sup>−1</sup>:** 3382 (br), 3057 (w), 3028 (w), 2954 (w), 2895 (w), 1493 (w), 1447 (w), 1434 (w), 1399 (w), 1314 (w), 1295 (w), 1261 (w), 1247 (m), 1187 (w), 1124 (m), 1079 (w), 1068 (w), 1034 (m), 1020 (m), 879 (w), 833 (s), 768 (m), 752 (m), 730 (s), 698 (s), 651 (m), 620 (m), 606 (m), 561 (w), 473 (w), 462 (m), 422 (w).

**HRMS:** Calcd. for C<sub>16</sub>H<sub>20</sub>OSi: 256.1278 [M]<sup>+</sup>; found (EI<sup>+</sup>): 256.1281

**mp:** 78 – 80 °C (hexanes/EtOAc)



### (3-Chlorophenyl)[2-(trimethylsilyl)phenyl]methanol (205)

To a nitrogen filled, flame-dried 100 mL RBF was added 1-bromo-3-chlorobenzene (2.0 mL, 17.0 mmol) along with dry THF (40 mL). The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and *n*-butyllithium (2.33 M in hexanes, 8.15 mL, 19.0 mmol) was added dropwise over 30 minutes. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for a further 30 mins, then 2-bromobenzaldehyde (2.50 mL, 21.5 mmol) was added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (20 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with  $\text{Et}_2\text{O}$  ( $3 \times 40\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to leave a viscous yellow oil (crude mass = 3.95 g). MeCN (30 mL) was added, followed by hexamethyldisilazane (HMDS, 1.95 mL, 9.3 mmol). The resulting solution was stirred for 15 mins at room temperature, then *N*-bromosuccinimide (NBS, 125 mg, 0.7 mmol) added in one portion. The temperature was adjusted to  $50\text{ }^{\circ}\text{C}$  and stirring maintained for a further 2 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (10 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a flame-dried,  $\text{N}_2$ -purged, 100 mL RBF. THF (15 mL) was added, and the solution cooled to  $-78\text{ }^{\circ}\text{C}$ . *n*-Butyllithium (1.6 M in hexanes, 5.94 mL, 9.5 mmol) was added by syringe over approximately 15 minutes, and the solution allowed to return to room temperature overnight. The mixture was quenched by the addition of  $\text{H}_2\text{O}$  (10 mL) and extracted into  $\text{Et}_2\text{O}$  ( $3 \times 20\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , concentrated under reduced pressure, and the resulting crude solid purified by column chromatography (eluent: 9:1 hexanes/ $\text{EtOAc}$ ) to afford the title compound as a pale yellow solid (2.06 g, 42%).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.59 (dd,  $J = 7.2, 1.5\text{ Hz}$ , 1H), 7.44 – 7.23 (m, 5H), 7.21 – 7.14 (m, 2H), 6.11 (d,  $J = 3.9\text{ Hz}$ , 1H), 2.11 (d,  $J = 4.0\text{ Hz}$ , 1H), 0.41 (s, 9H).

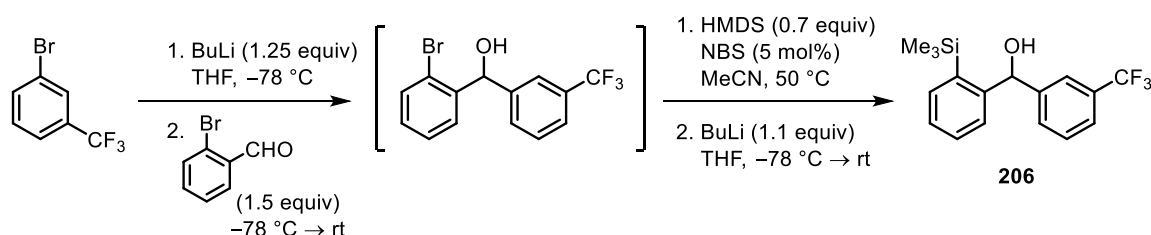
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  148.9, 145.9, 139.1, 134.7, 134.4, 130.2, 129.6, 128.2, 127.7, 127.4, 126.8, 124.9, 74.2, 0.9.



$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ : 3242 (br), 3062 (w), 2953 (w), 2895 (w), 1595 (w), 1573 (w), 1472 (w), 1425 (m), 1405 (w), 1304 (w), 1247 (m), 1185 (m), 1124 (m), 1096 (w), 1070 (w), 1032 (m), 887 (w), 875 (w), 835 (m), 778 (m), 769 (m), 721 (m), 686 (m), 651 (m), 622 (m), 607 (m), 573 (w), 473 (w), 430 (w), 417 (w).

**HRMS:** Calcd. for  $\text{C}_{16}\text{H}_{19}\text{O}^{35}\text{ClSi}$ : 290.0888  $[\text{M}]^+$ ; found ( $\text{EI}^+$ ): 290.0902

**mp:** 100 – 102 °C (hexanes/EtOAc)



### [3-(Trifluoromethyl)phenyl][2-(trimethylsilyl)phenyl]methanol (206)

To a flame-dried Schlenk flask (under an atmosphere of  $\text{N}_2$ ) was added 1-bromo-3-(trifluoromethyl)benzene (2.8 mL, 20.0 mmol) along with dry THF (50 mL). The solution was cooled to  $-78\text{ }^\circ\text{C}$  and *n*-butyllithium (2.33 M in hexanes, 8.58 mL, 20.0 mmol) was added dropwise over 30 minutes. The mixture was stirred at  $-78\text{ }^\circ\text{C}$  for a further 30 mins, then 2-bromobenzaldehyde (2.50 mL, 21.5 mmol) was added *via* syringe. The flask was removed from the cold bath and allowed to return to room temperature overnight. Water (40 mL) was added to quench any remaining organolithium species, and the aqueous layer extracted with EtOAc ( $3 \times 40\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to leave a viscous orange oil. MeCN (40 mL) was added, followed by hexamethyldisilazane (HMDS, 2.33 mL, 11.2 mmol). The resulting solution was stirred for 15 mins at room temperature, then *N*-bromosuccinimide (NBS, 140 mg, 0.8 mmol) added in one portion. The temperature was adjusted to  $50\text{ }^\circ\text{C}$  and stirring maintained for a further 2 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (20 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a flame-dried,  $\text{N}_2$ -purged, 100 mL RBF. THF (40 mL) was added, and the solution cooled to  $-78\text{ }^\circ\text{C}$ . *n*-Butyllithium (2.33 M in hexanes, 6.87 mL, 16.0 mmol) was added by syringe over approximately 15 minutes, and the solution allowed to return to room temperature overnight.

The mixture was quenched by the addition of H<sub>2</sub>O (40 mL) and extracted into EtOAc (3 × 40 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and the resulting crude solid purified by column chromatography (eluent: 19:1 hexanes/EtOAc) to afford the title compound as a white solid (3.36 g, 52%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.73 – 7.70 (m, 1H), 7.61 – 7.57 (m, 1H), 7.56 – 7.50 (m, 1H), 7.47 – 7.40 (m, 2H), 7.38 – 7.29 (m, 2H), 7.16 – 7.11 (m, 1H), 6.17 (d, *J* = 3.9 Hz, 1H), 2.11 (d, *J* = 3.9 Hz, 1H), 0.41 (s, 9H).

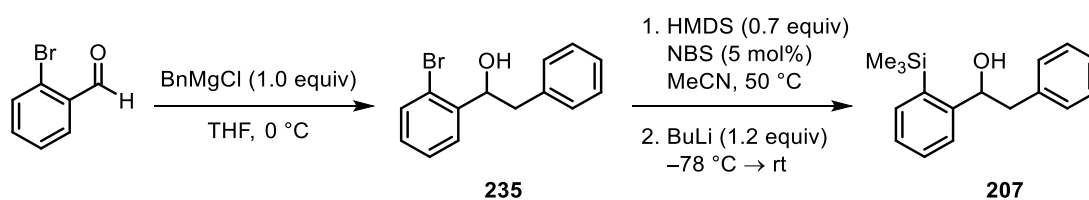
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 148.7, 144.7, 139.0, 134.7, 130.6 (q, *J* = 31.6 Hz), 130.1, 130.0 – 129.9 (m), 128.5, 128.4, 127.7, 124.2 (q, *J* = 273.0 Hz), 123.9 (q, *J* = 3.8 Hz), 123.1 (q, *J* = 3.9 Hz), 74.1, 0.7.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ –62.55 (s)

**ν<sub>max</sub>(neat)/cm<sup>–1</sup>:** 3292 (br), 2962 (w), 1448 (w), 1435 (w), 1327 (m), 1251 (m), 1176 (m), 1157 (m), 1118 (s), 1096 (m), 1070 (m), 1027 (m), 906 (w), 889 (w), 836 (s), 796 (m), 776 (m), 753 (m), 730 (m), 708 (m), 699 (m), 673 (m), 651 (m), 623 (m), 607 (m), 556 (w), 470 (w), 450 (w), 420 (w).

**HRMS:** Calcd. for C<sub>17</sub>H<sub>19</sub>OF<sub>3</sub>Si: 324.1152 [M]<sup>+</sup>; found (EI<sup>+</sup>): 324.1148

**mp:** 100–101 °C (hexanes/EtOAc)



### 1-(2-Bromophenyl)-2-phenylethan-1-ol (235)

Benzylmagnesium chloride (2.0 M in THF, 10.0 mL, 20.0 mmol) was added to a flame-dried Schlenk tube (under a N<sub>2</sub> atmosphere) and diluted with dry THF (10 mL). The mixture was cooled to 0 °C, then 2-Bromobenzaldehyde (2.35 mL, 20.0 mmol) was added dropwise *via* syringe over approximately 10 minutes. Following addition, the mixture was stirred at room temperature for 1 hour, then poured into ice (approx. 50 g). 10% w/w HCl was added until all of the white precipitate had dissolved, then Et<sub>2</sub>O (30 mL) added, the layers separated, and the

aqueous layer further extracted with Et<sub>2</sub>O (3 × 30 mL). The combined organic extracts were washed with brine (2 × 30 mL), dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The resulting crude yellow oil was purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a viscous, colourless oil (1.54 g, 28%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.61 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39 – 7.24 (m, 6H), 7.16 (ddd, *J* = 8.0, 7.3, 1.8 Hz, 1H), 5.27 (dt, *J* = 9.4, 3.1 Hz, 1H), 3.21 (dd, *J* = 13.8, 3.0 Hz, 1H), 2.74 (dd, *J* = 13.8, 9.4 Hz, 1H), 1.99 (d, *J* = 3.3 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 143.0, 138.3, 132.8, 129.6, 129.0, 128.8, 127.9, 127.4, 126.9, 121.9, 74.2, 44.5.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3306 (br w), 3026 (w), 2947 (w), 1495 (m), 1467 (m), 1452 (m), 1437 (m), 1253 (w), 1200 (w), 1117 (w), 1077 (m), 1056 (m), 1047 (m), 1035 (m), 1022 (m), 1002 (m), 943 (w), 863 (w), 850 (w), 746 (s), 716 (m), 701 (m), 678 (m), 649 (m), 619 (w), 567 (m), 508 (w), 475 (w), 443 (w).

<sup>1</sup>H and <sup>13</sup>C NMR data are consistent with those reported in the literature.<sup>23</sup>

### 2-phenyl-1-[2-(trimethylsilyl)phenyl]ethan-1-ol (207)

To a flame-dried, N<sub>2</sub>-purged round-bottomed flask was added 1-(2-bromophenyl)-2-phenylethan-1-ol (1.42 g, 5.1 mmol) and MeCN (10 mL), followed by hexamethyldisilazane (HMDS, 0.73 mL, 3.5 mmol). The resulting solution was stirred for 15 mins at room temperature, then *N*-bromosuccinimide (NBS, 45 mg, 0.25 mmol) added in one portion. The temperature was adjusted to 50 °C and stirring maintained for a further 2 hours. The reaction mixture was then concentrated under reduced pressure, diluted with hexane (10 mL), and washed through a short plug of silica. The resulting solution was then concentrated *in vacuo*, and the crude oil transferred to a flame-dried, N<sub>2</sub>-purged, 50 mL RBF (crude mass = 0.70 g). THF (6 mL) was added, and the solution cooled to -78 °C. *n*-Butyllithium (1.6 M in hexanes, 2.00 mL, 3.2 mmol) was added by syringe over approximately 10 minutes, and the solution allowed to return to room temperature overnight. The mixture was quenched by the addition of H<sub>2</sub>O (5 mL) and extracted into EtOAc (3 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and the resulting crude oil purified by column chromatography (eluent: 9:1 hexanes/EtOAc) to afford the title compound as a viscous colourless oil (0.45 g, 33%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.74 – 7.69 (m, 1H), 7.57 – 7.46 (m, 2H), 7.40 – 7.27 (m, 6H), 5.18 (ddd, *J* = 8.6, 4.6, 2.4 Hz, 1H), 3.13 – 3.01 (m, 2H), 1.91 (d, *J* = 2.4 Hz, 1H), 0.38 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 149.7, 138.6, 137.6, 134.5, 129.9, 129.6, 128.8, 127.4, 126.8, 126.2, 74.3, 45.8, 1.0.

***v*<sub>max</sub>(neat)/cm<sup>-1</sup>:** 3401 (br), 3057 (w), 3027 (w), 2950 (w), 1495 (w), 1453 (w), 1432 (w), 1249 (m), 1122 (w), 1079 (w), 1032 (w), 999 (w), 834 (m), 789 (w), 762 (m), 728 (m), 698 (m), 622 (w), 551 (w), 467 (w).

**HRMS:** Calcd. for C<sub>17</sub>H<sub>22</sub>OSi: 270.1435 [M]<sup>+</sup>; found (EI<sup>+</sup>): 270.1434

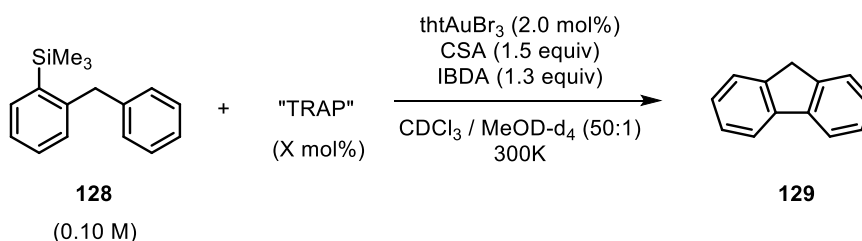
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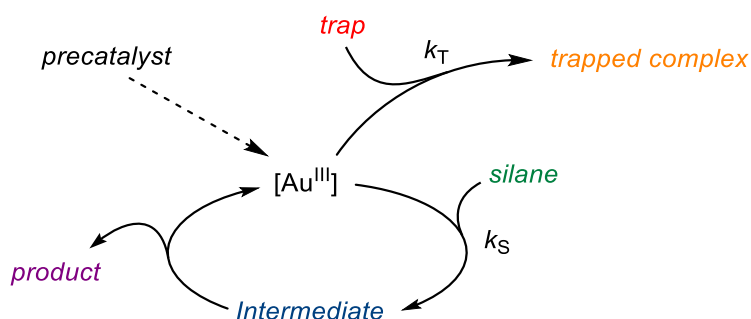
## Appendix A

All trapping competition experiments were performed against the gold-catalysed intramolecular cyclisation of **128** to form **129** (Scheme A1).

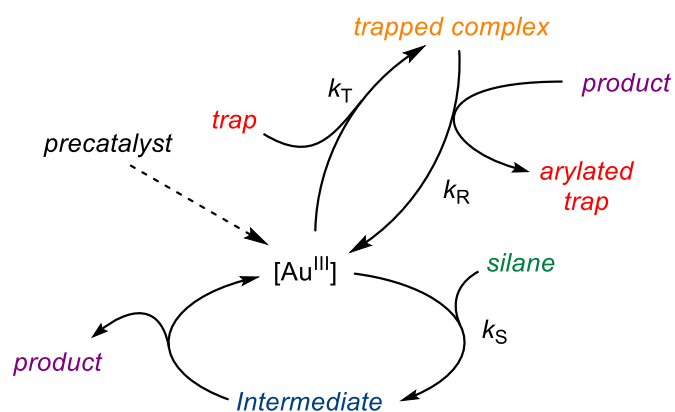


**Scheme A1.** Cyclisation of **128** to form **129**, monitored by *in situ*  $^1\text{H}$  NMR.

The following concentration-time profiles display the formation of product (**129**) across a range of different trap concentrations, as referenced in each figure. Reactions were monitored by *in situ*  $^1\text{H}$  NMR following the procedure described in Section 5.21. Simulated kinetic data (blue lines) was generated by fitting to either Model A or B as denoted in each case, and is plotted against experimental data (white circles) for comparison.

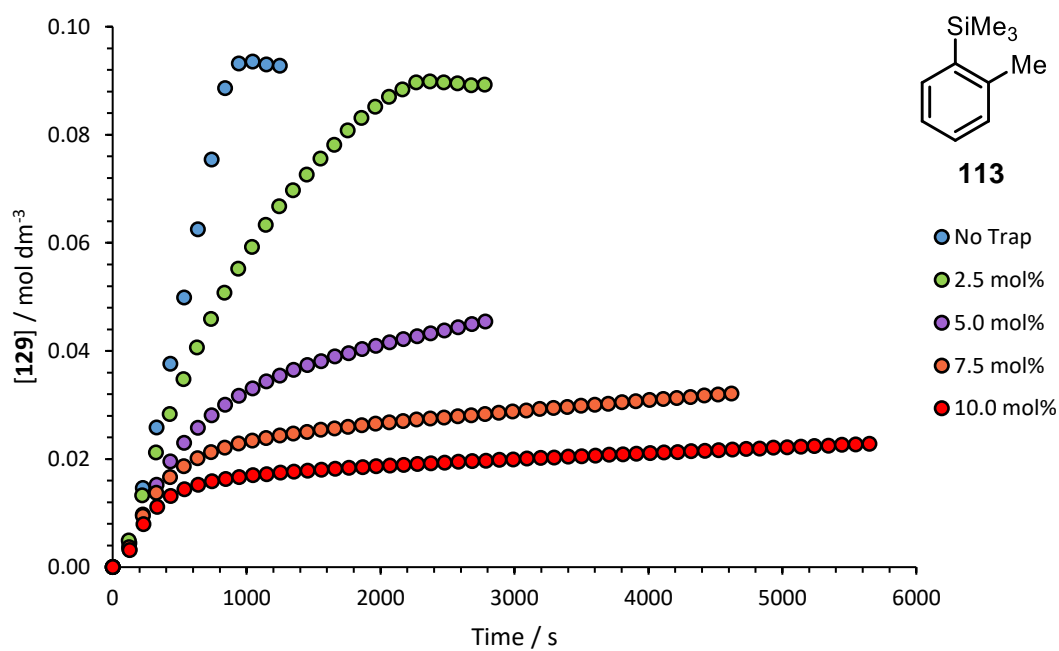


**Scheme A2.** Visual representation of Model A.



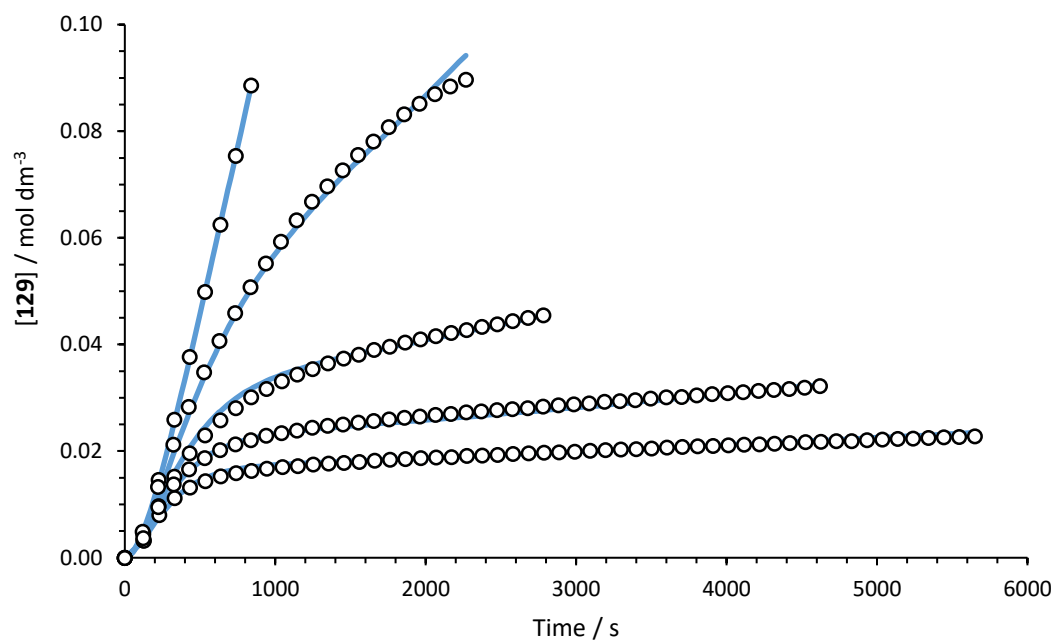
**Scheme A3.** Visual representation of Model B.

### Trapping by (2-methylphenyl)trimethylsilane (**113**)



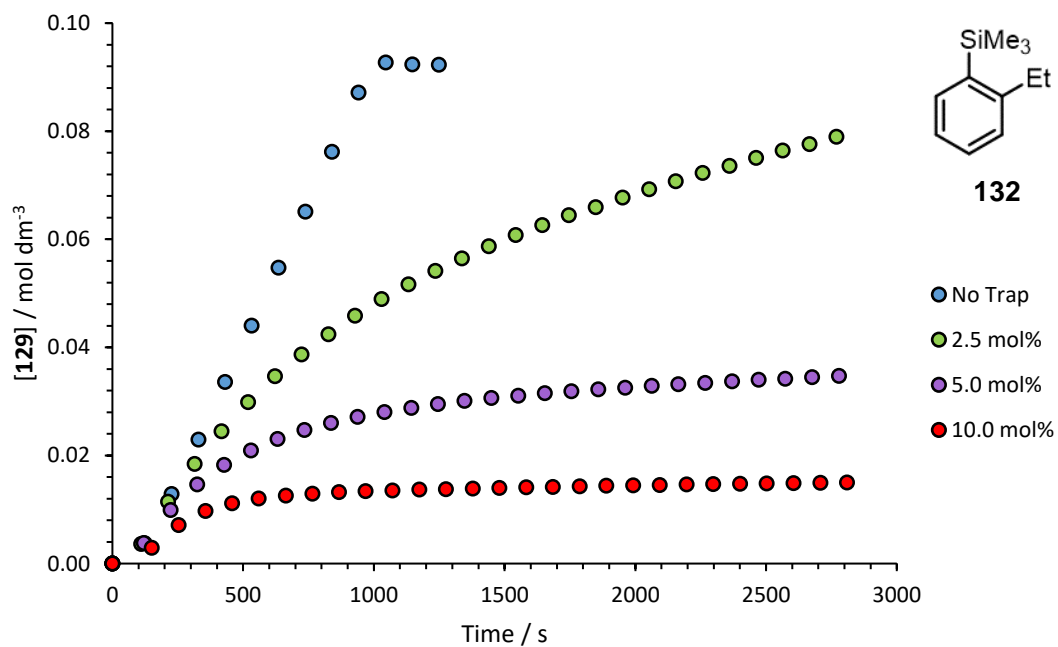
**Figure A1.** Concentration-time profile for trapping by arylsilane **113**.



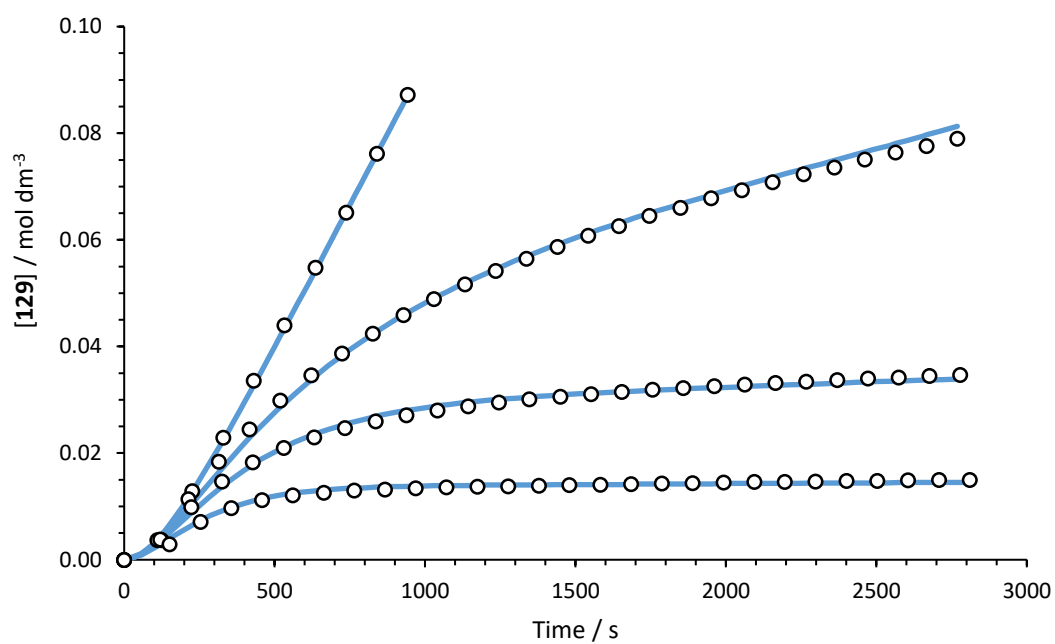


**Figure A2.** Simulated kinetic fitting for trapping by arylsilane **113** using Model B.

#### Trapping by (2-ethylphenyl)trimethylsilane (**132**)

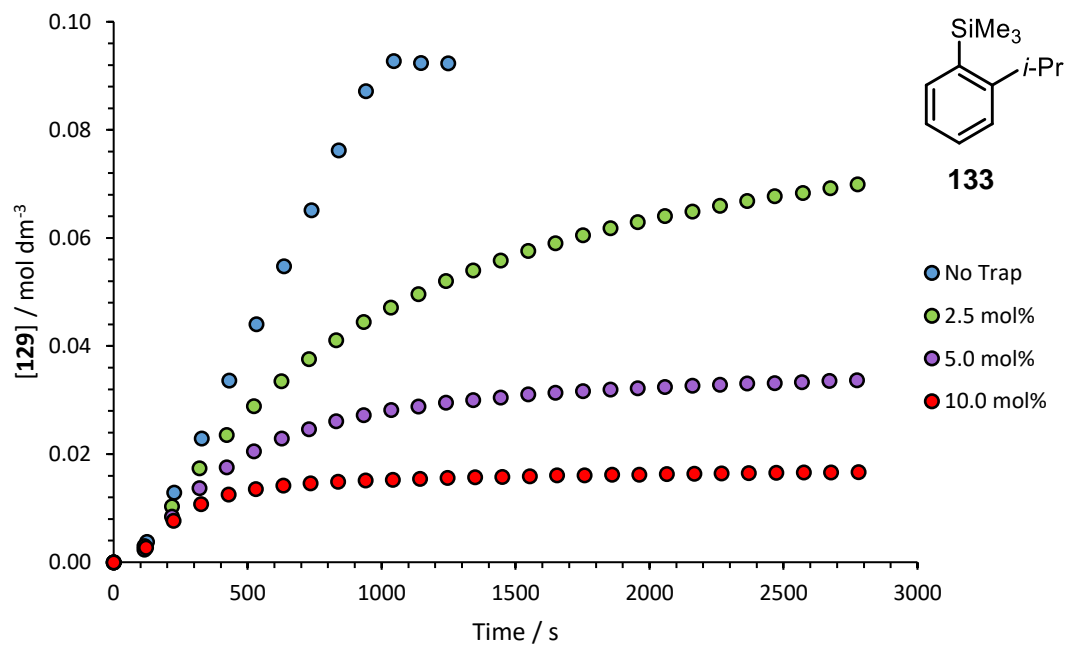


**Figure A3.** Concentration-time profile for trapping by arylsilane **132**.

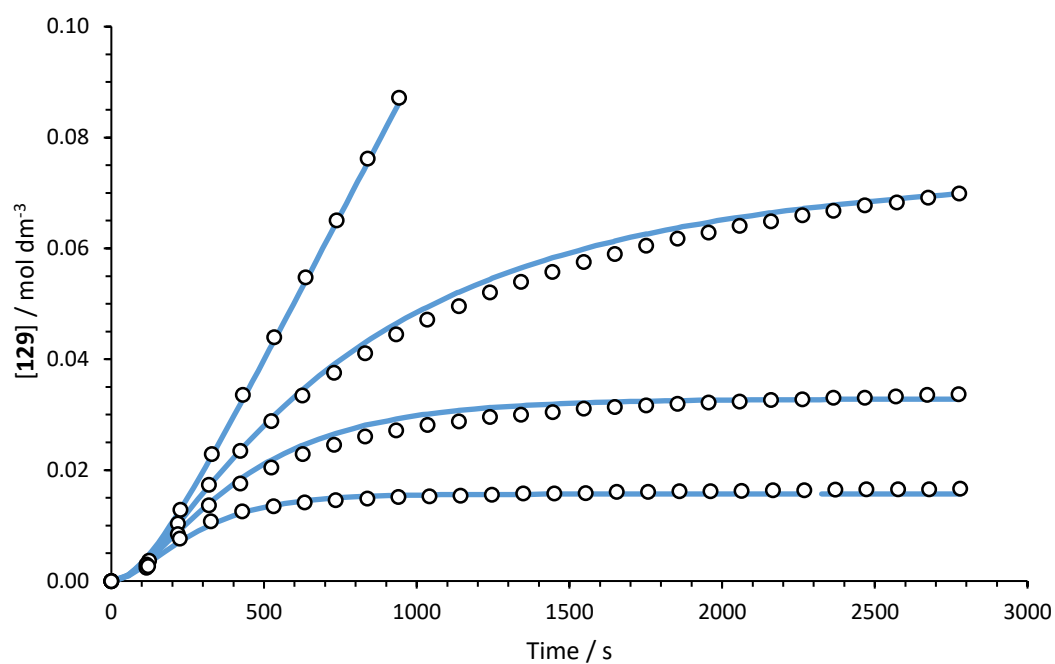


**Figure A4.** Simulated kinetic fitting for trapping by arylsilane **132** using Model B.

#### Trapping by (2-*iso*-propylphenyl)trimethylsilane (**133**)

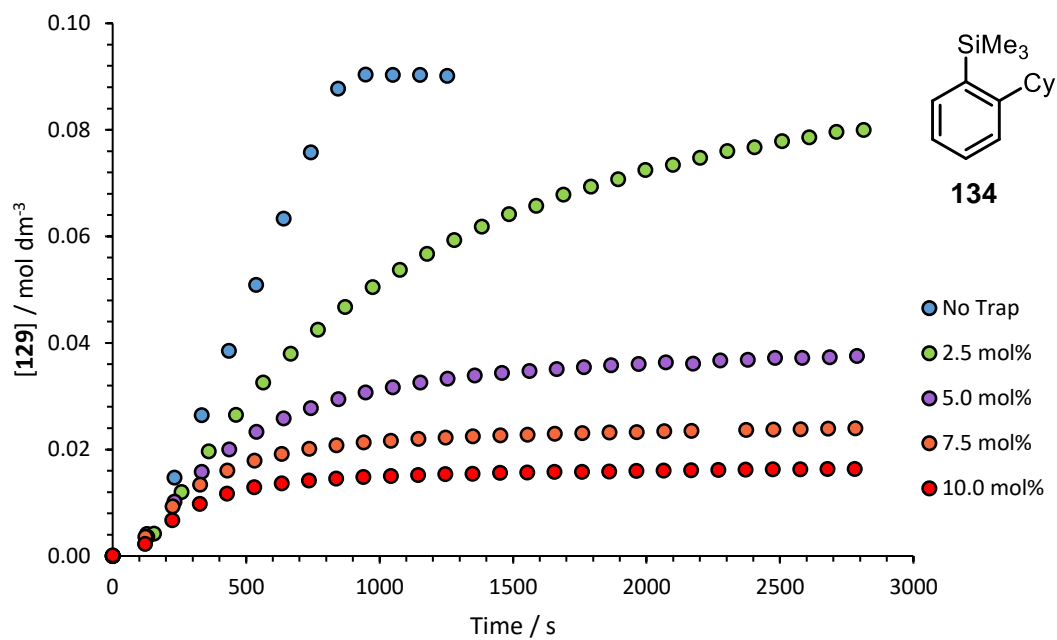


**Figure A5.** Concentration-time profile for trapping by arylsilane **133**.

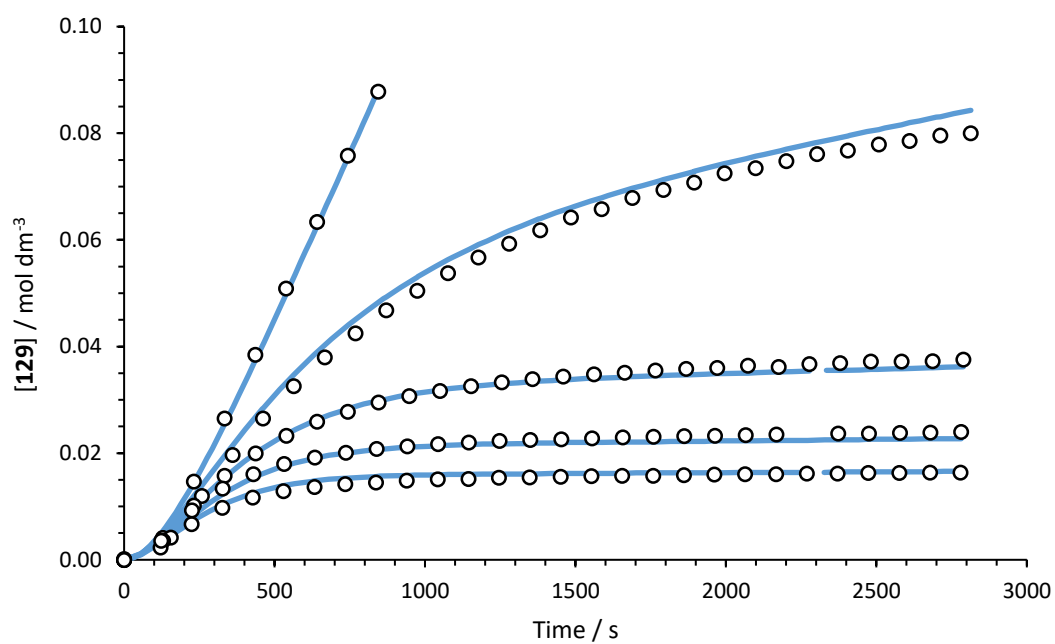


**Figure A6.** Simulated kinetic fitting for trapping by arylsilane **133** using Model B.

**Trapping by (2-cyclohexylphenyl)trimethylsilane (**134**)**

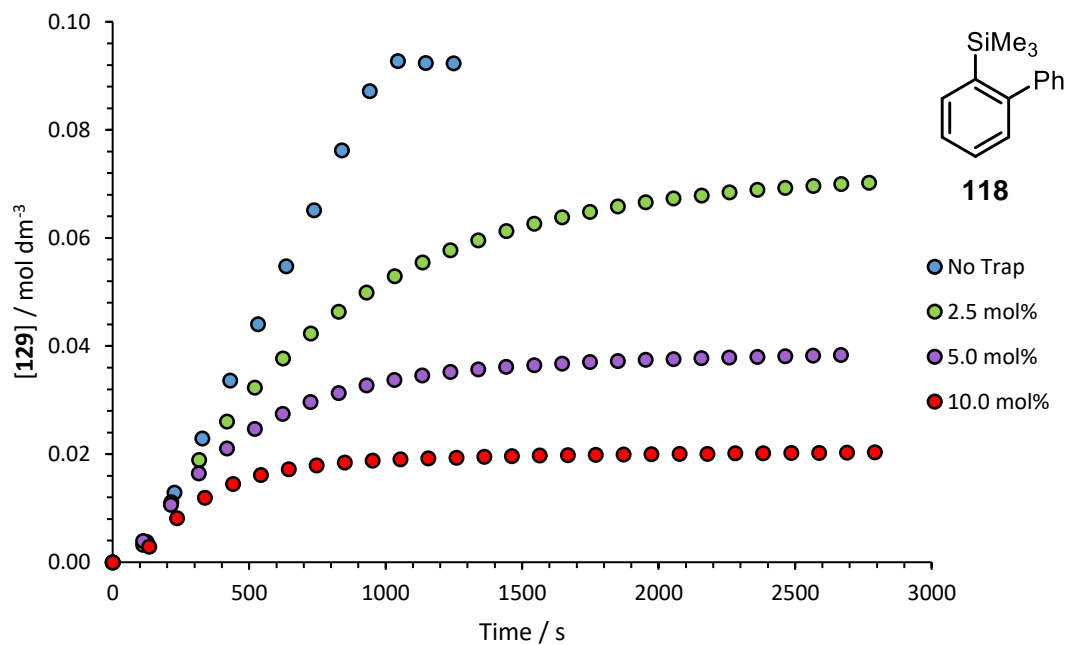


**Figure A7.** Concentration-time profile for trapping by arylsilane **134**.

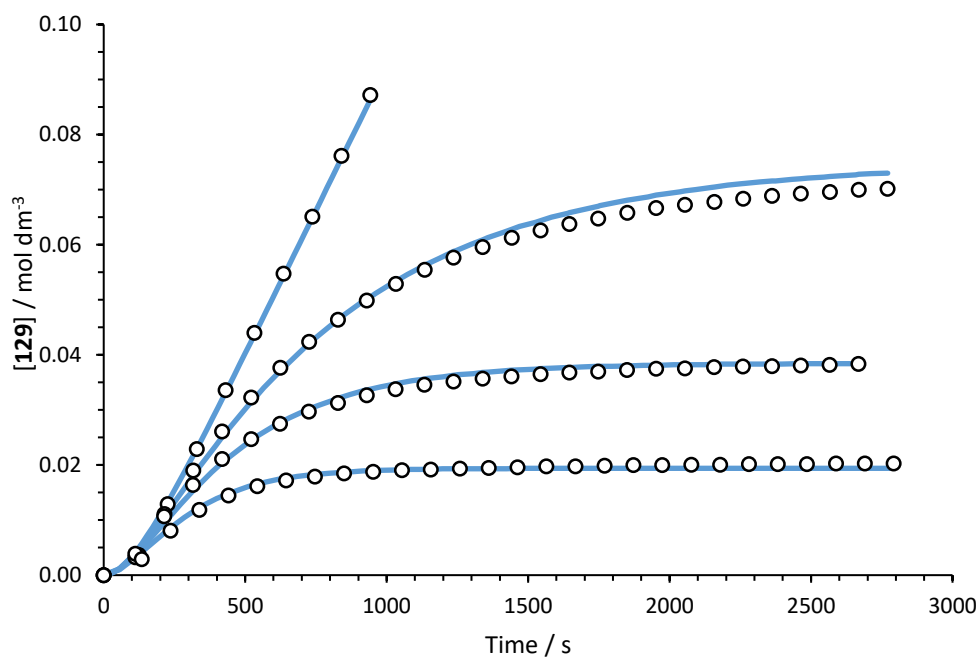


**Figure A8.** Simulated kinetic fitting for trapping by arylsilane **134** using Model B.

#### Trapping by (2-biphenyl)trimethylsilane (**118**)

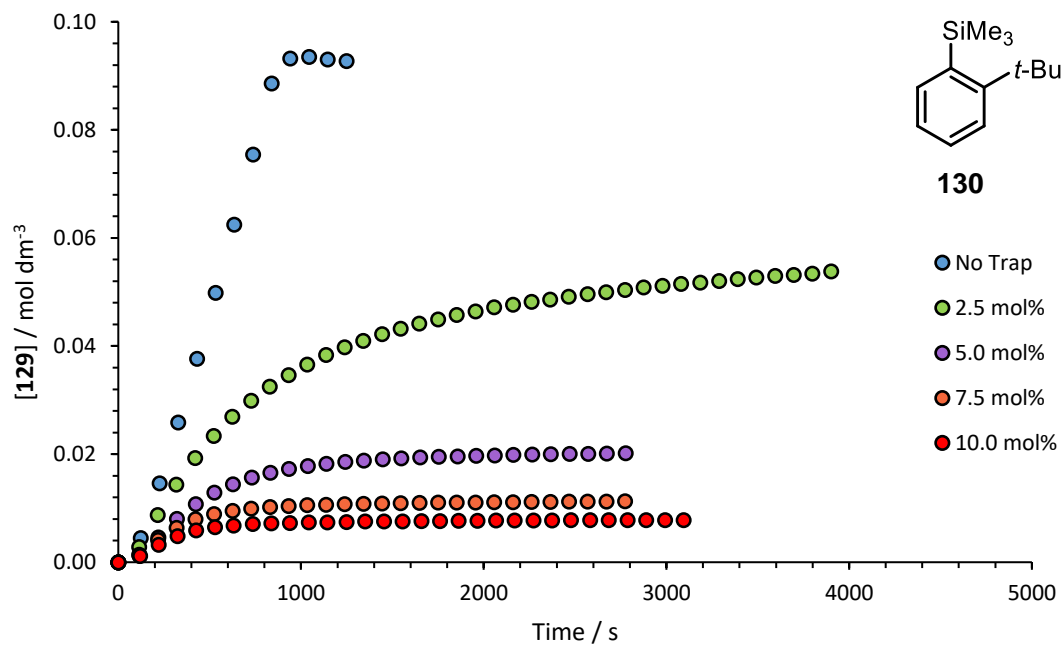


**Figure A9.** Concentration-time profile for trapping by arylsilane **118**.

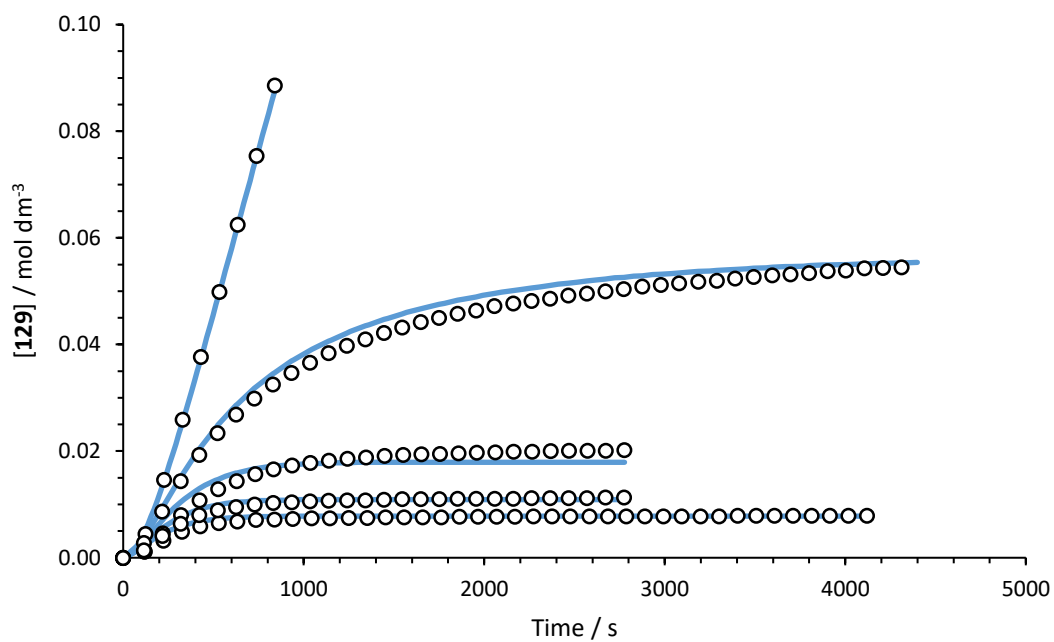


**Figure A10.** Simulated kinetic fitting for trapping by arylsilane **118** using Model A.

#### Trapping by (2-*tert*-butylphenyl)trimethylsilane (**130**)

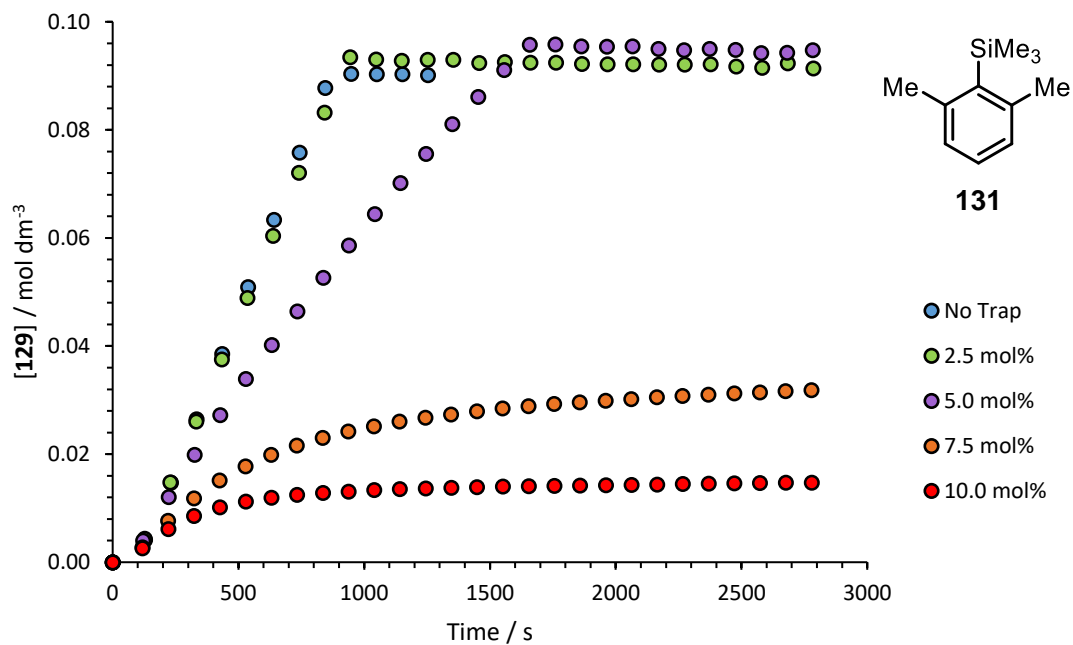


**Figure A11.** Concentration-time profile for trapping by arylsilane **130**.

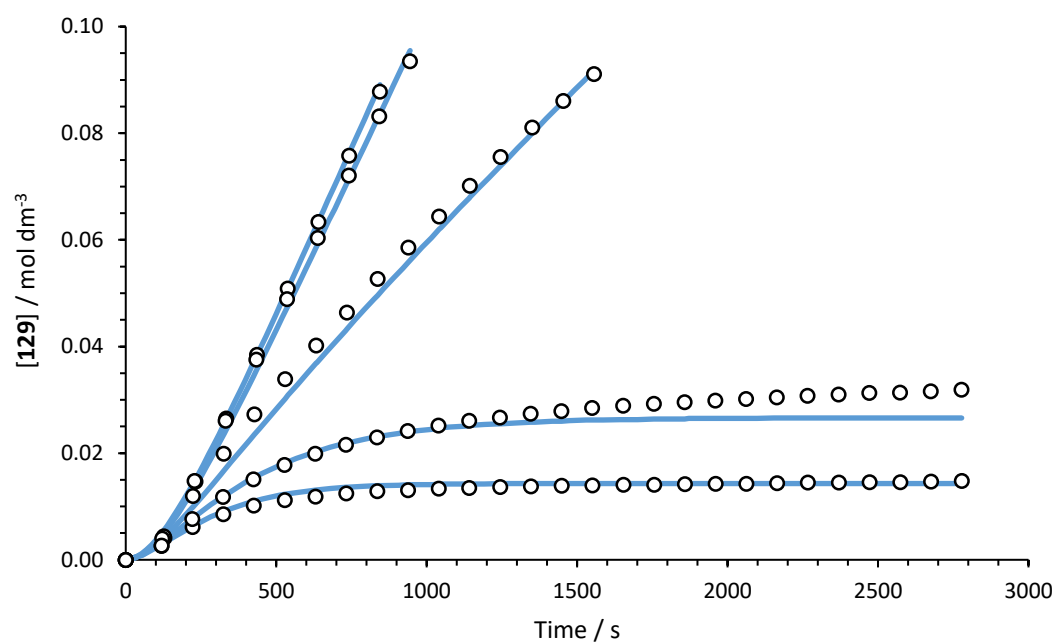


**Figure A12.** Simulated kinetic fitting for trapping by arylsilane **130** using Model A.

**Trapping by (2,6-dimethylphenyl)trimethylsilane (**131**)**

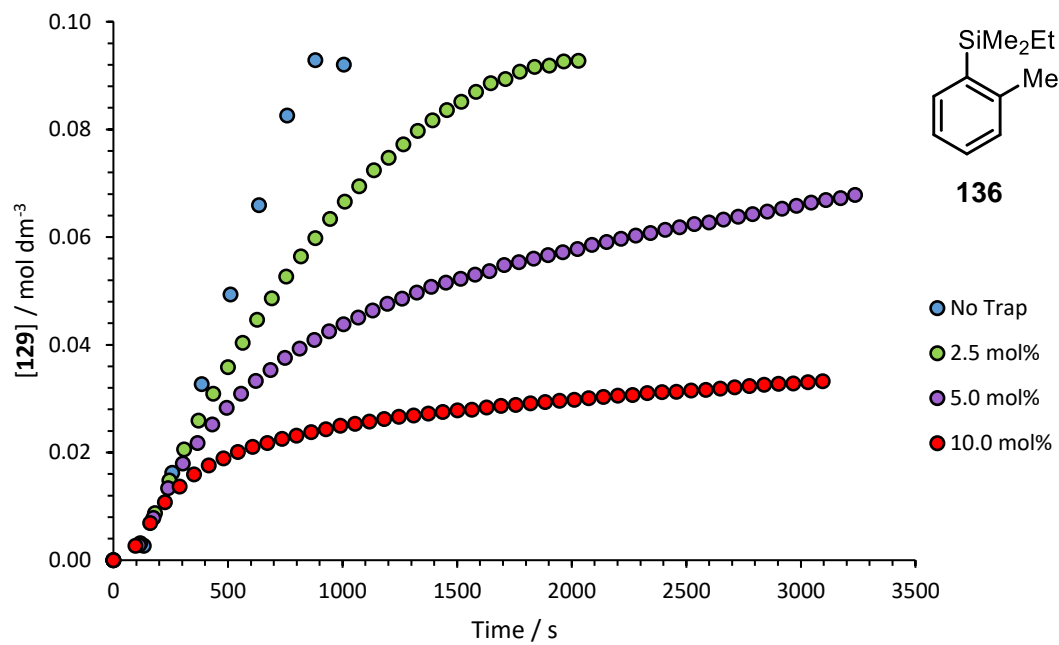


**Figure A13.** Concentration-time profile for trapping by arylsilane **131**.

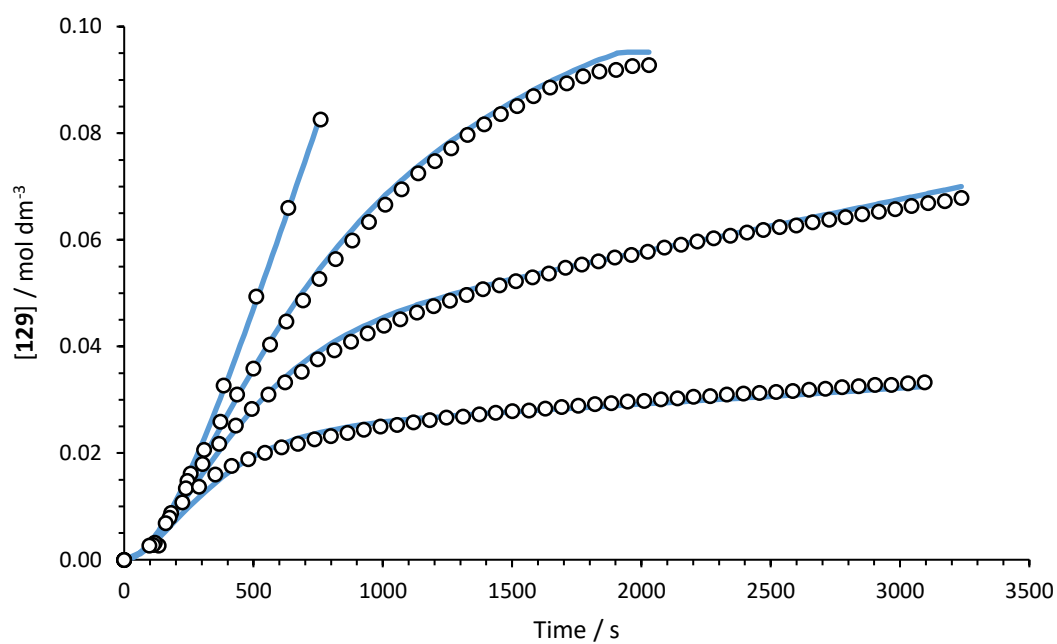


**Figure A14.** Simulated kinetic fitting for trapping by arylsilane **131** using Model A.

**Trapping by (2-methylphenyl)ethyldimethylsilane (**136**)**

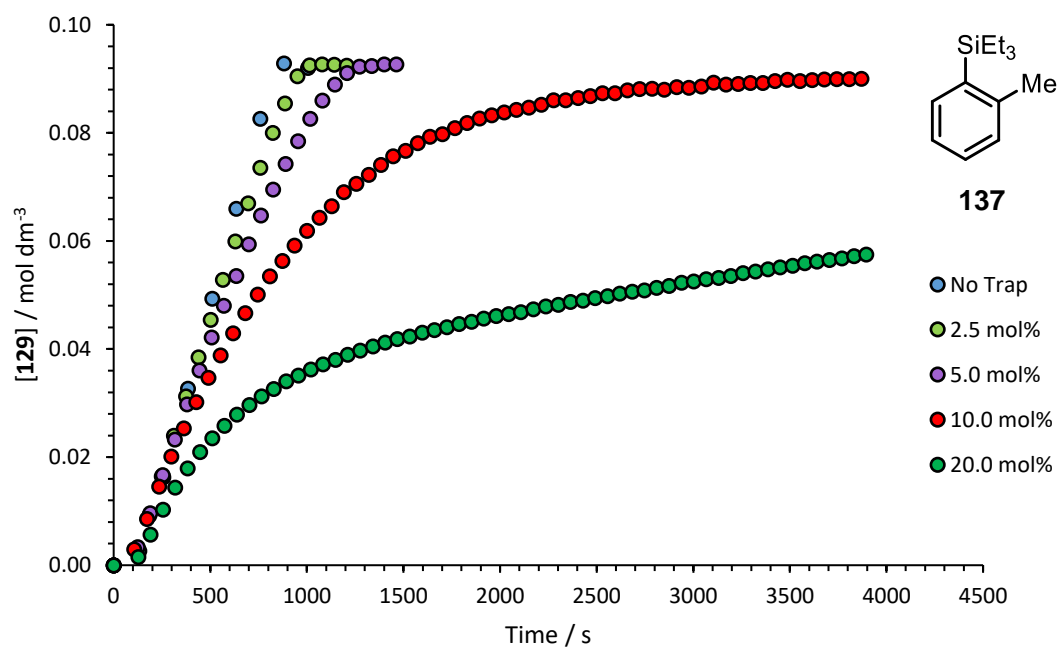


**Figure A15.** Concentration-time profile for trapping by arylsilane **136**.



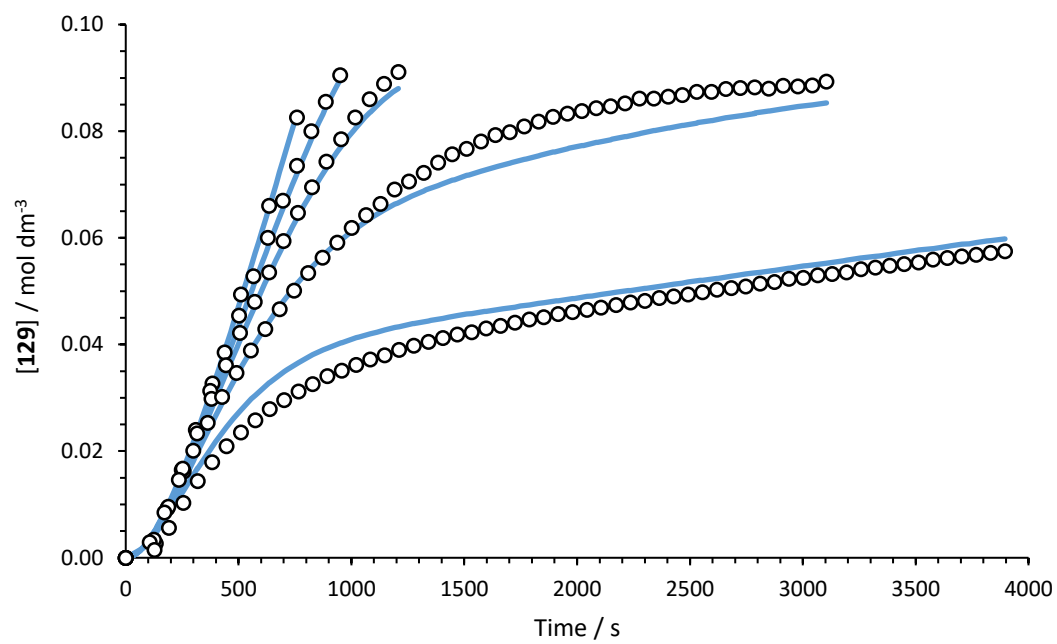
**Figure A16.** Simulated kinetic fitting for trapping by arylsilane **136** using Model B.

#### Trapping by (2-methylphenyl)triethylsilane (**137**)



**Figure A17.** Concentration-time profile for trapping by arylsilane **137**.

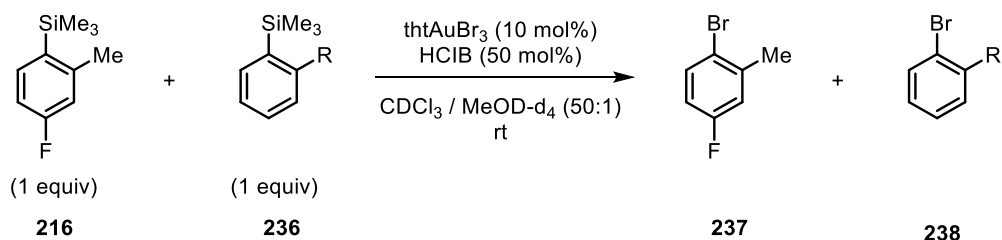




**Figure A18.** Simulated kinetic fitting for trapping by arylsilane **137** using Model B.

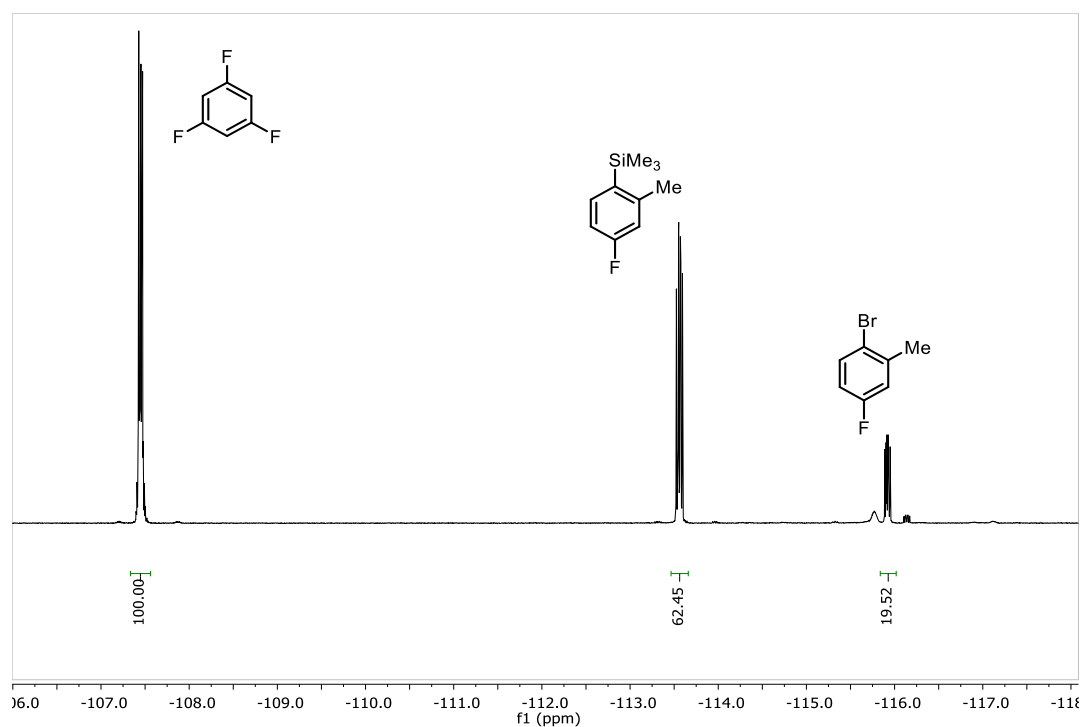
## Appendix B

The relative rates of bromodesilylation for a number of arylsilane traps were determined experimentally in order to reduce the number of variables to be fitted in the kinetic model. A stoichiometric competition experiment using the tetrahydrothiophene derived pre-catalyst was performed to ensure that the conditions were as close to those used for catalysis as possible (Scheme B1).



**Scheme B1.** Stoichiometric competition experiment to determine relative rates of bromodesilylation.

The amount of trap that was brominated in each case was calculated based on the amount of **237** detected (by quantitative <sup>19</sup>F NMR, against an internal standard). In the absence of any added trap, unreacted arylsilane (**216**) and bromodesilylated product (**237**) (0.0195 mmol, 19.5 mol%) were detected, consistent with the loss of two bromide ligands from the catalyst, fully sequestered by the arylsilane reagent (Figure B1). The reproducibility of the experiment was confirmed by a number of repeat reactions, and the observed deviation typically within  $\pm 0.1$  mol%.



**Figure B1.**  $^{19}\text{F}$  NMR spectra of the crude reaction mixture (Entry 1, Table B1).

The relative rates of bromodesilylation for the series of arylsilane reagents are summarised in Table B1. The values are normalised against the *ortho*-benzyl substituent (**128**) such that the relative rate constants ( $k_{\text{T-Br}}/k_{\text{S-Br}}$ ) can be used directly in the kinetic model for catalyst trapping.

**Table B1.** Summary of bromodesilylation experiments for a series of arylsilane traps.

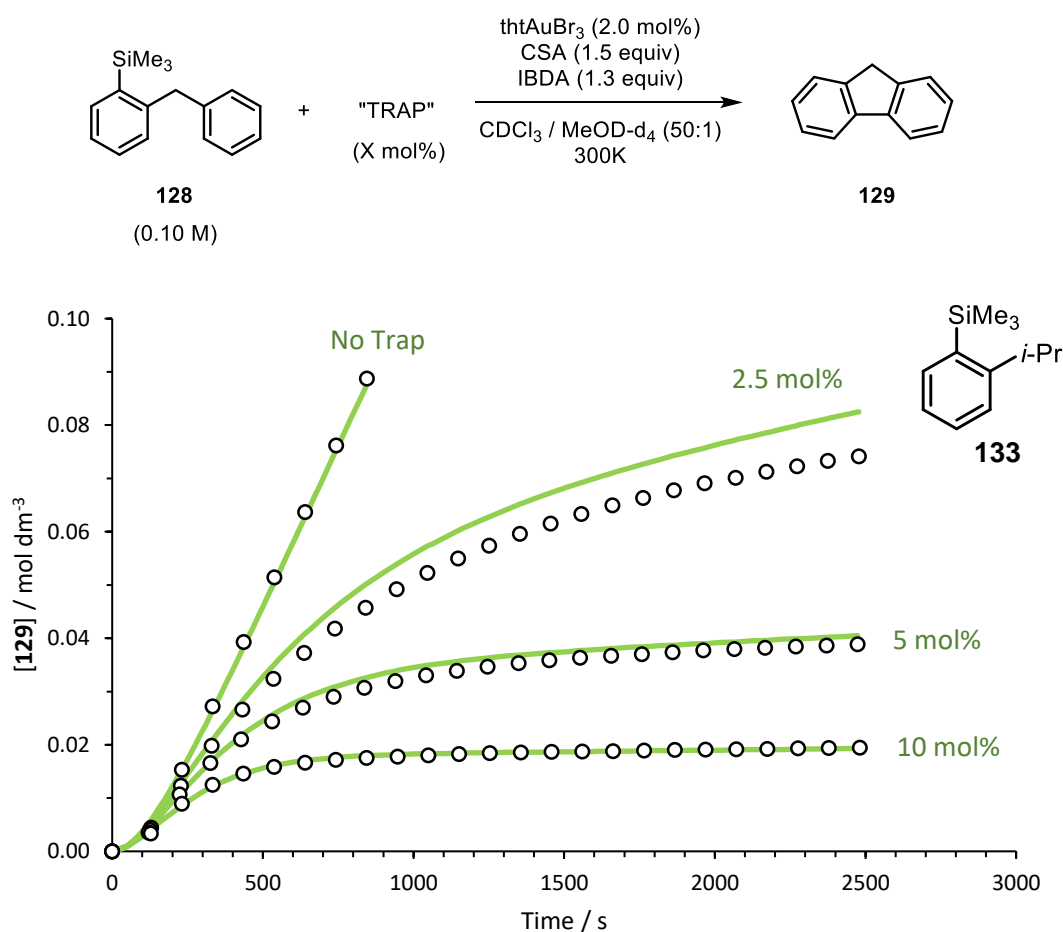
R	<b>237</b> formed (mmol)	$k_{236}/k_{216}$	$k_{\text{T-Br}}/k_{\text{S-Br}}$
-	0.0195 <sup>a</sup>	-	-
Me ( <b>113</b> )	0.0050 <sup>b</sup>	3.0	<b>3.3</b>
Et ( <b>132</b> )	0.0048 <sup>b</sup>	3.2	<b>3.6</b>
<i>i</i> -Pr ( <b>133</b> )	0.0051	2.9	<b>3.2</b>
Cy ( <b>134</b> )	0.0052	2.8	<b>3.1</b>
Bn ( <b>128</b> )	0.0104 <sup>b</sup>	0.9	<b>1.0</b>
Ph ( <b>118</b> )	0.0142 <sup>b</sup>	0.4	<b>0.4</b>

[a] Average of three repeat experiments. [b] Average of two repeat experiments.

## Appendix C

The concentration-time profile for catalyst trapping proved highly sensitive to small changes in catalyst and trap concentration (particularly at low initial trap concentrations), and therefore required careful sample preparation to ensure that good fitting simulations could be generated. The use of stock solutions (made to known concentrations) allowed accurate measurement of the required amounts of each component, minimising the degree of error in the initial concentrations used.

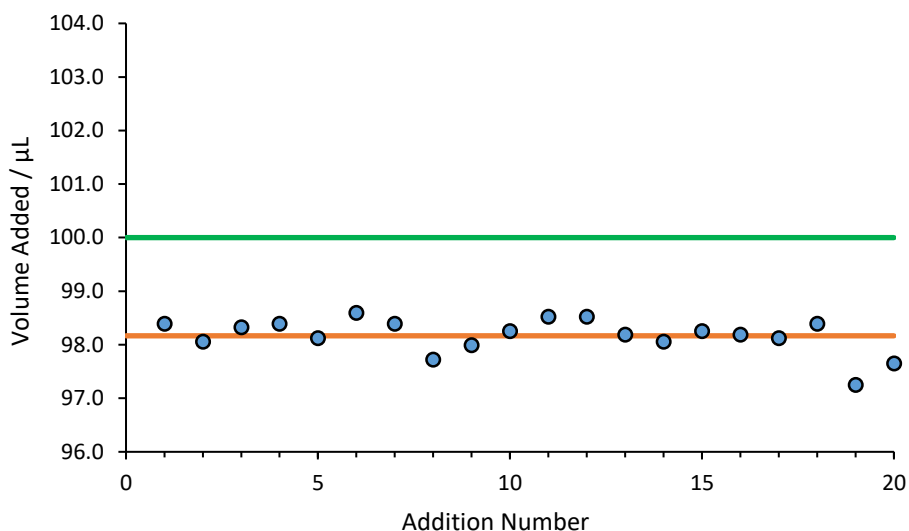
However, initial attempts to prepare samples by combining aliquots from three separate stock solutions (substrate, trap, and catalyst) resulted in consistently unsatisfactory simulations (Scheme C1).



**Scheme C1.** Attempted trapping and kinetic modelling experiment for **133**.

The observation that low trap concentrations were particularly difficult to simulate suggested that the initial concentrations used in the kinetic model might be inaccurate. During the course

of trying to identify the source of this experimental error, we noted a disparity between the desired, and actual, dosage of stock solutions using microlitre syringes. When attempting to add 100  $\mu\text{L}$  chloroform to a screw-capped vial, a consistent and systematic under-dosage (by weight) was observed (Figure C1).



**Figure C1.** Attempted addition of 100  $\mu\text{L}$  aliquots to a screw-capped vial. Volume added was determined based on the weight change of the vial between additions.

This effect proved general (for chloroform) across a range of syringe designs and sizes and was confirmed by blind testing carried out by a number of colleagues. Other solvents appeared to have different associated systematic errors, some overestimates and others underestimates, though were not investigated in detail. Our present assumption is that the syringes are calibrated for use with  $\text{H}_2\text{O}$ , and therefore small inaccuracies resulting from differences in solvent properties (eg. viscosity, surface tension) can be expected.

In this case, the small (but cumulative) error was sufficient to cause poorly fitting simulations. This could be mitigated by using fewer stock solutions (the substrate and catalyst were added from one solution) and calculating the amount of trap added by measuring the weight of stock solution used. The details of this optimised procedure are provided in Section 5.2.3.